VOLUME 61 • APRIL 1959 • NUMBER 4

AMA ARCHIVES OF OPHTHALMOLOGY

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David Barsky

Arcus Senilis
David G. Cogan and Toichiro Kuwabara

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J. H. Wania and F. B. Walsh

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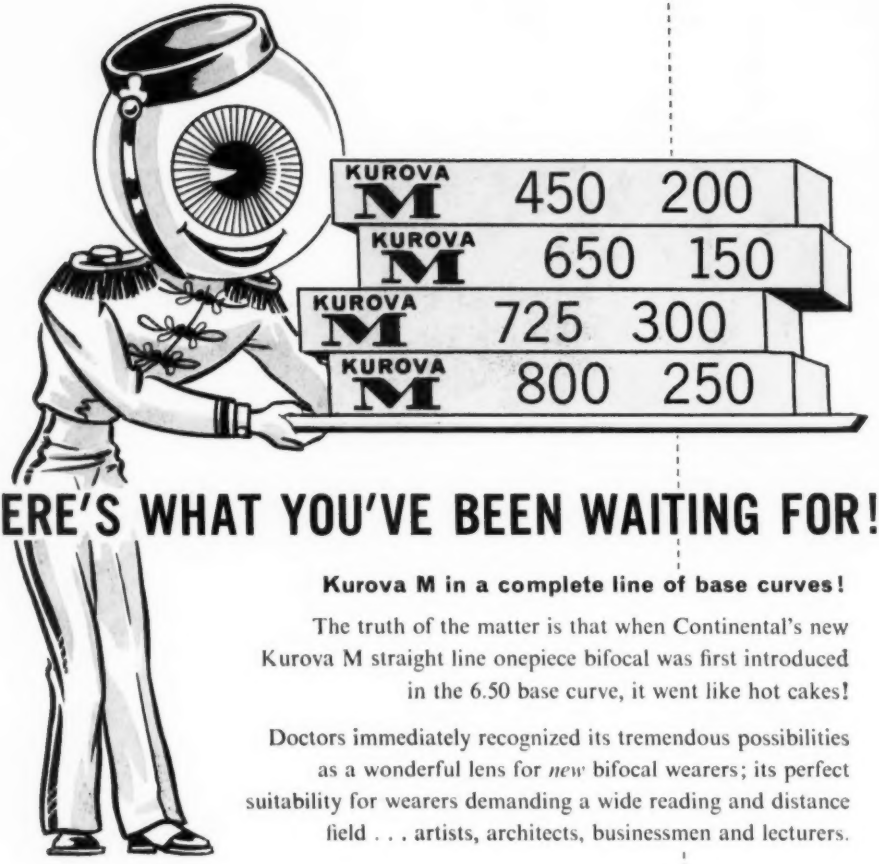

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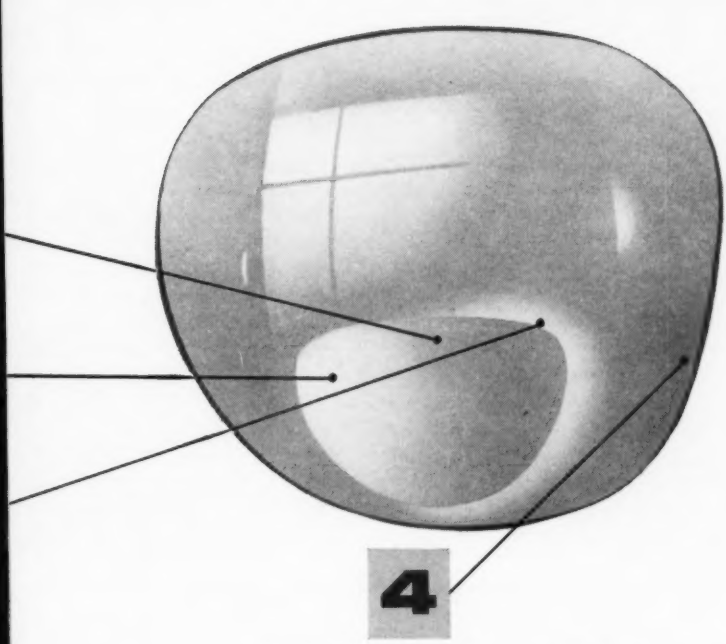

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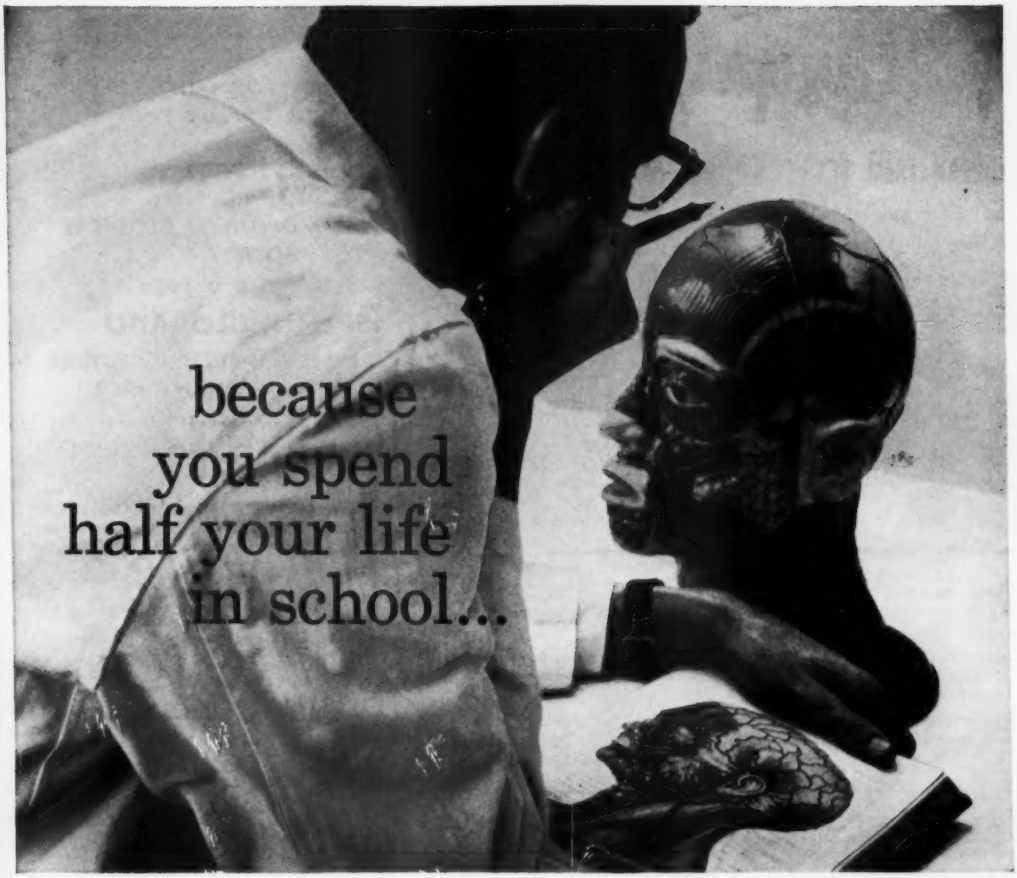

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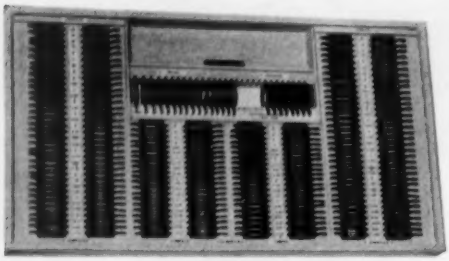

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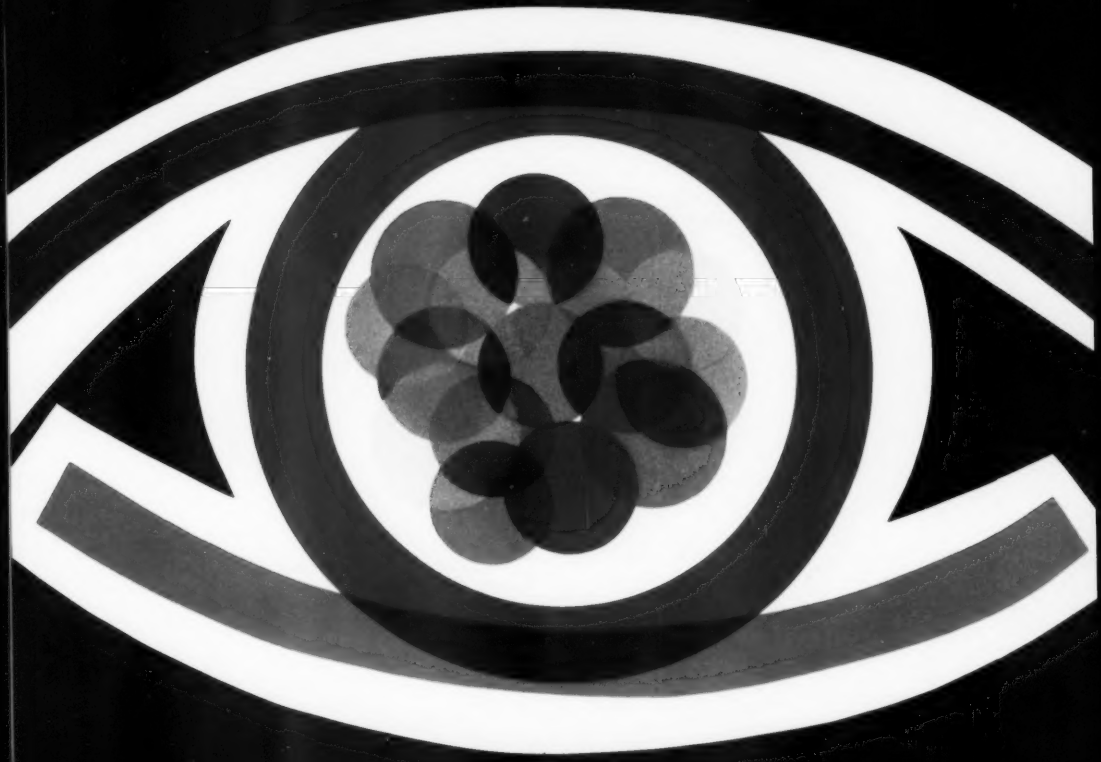

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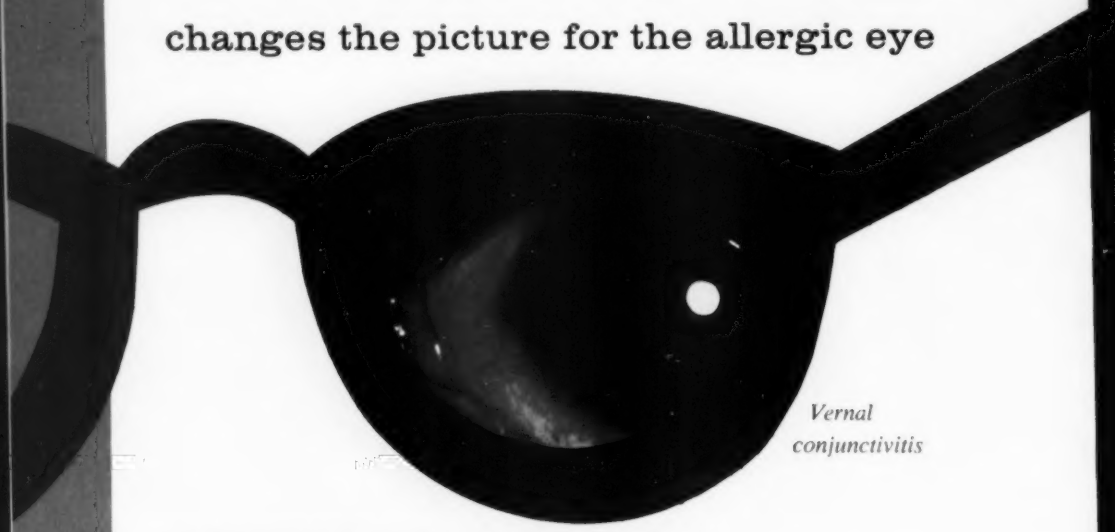

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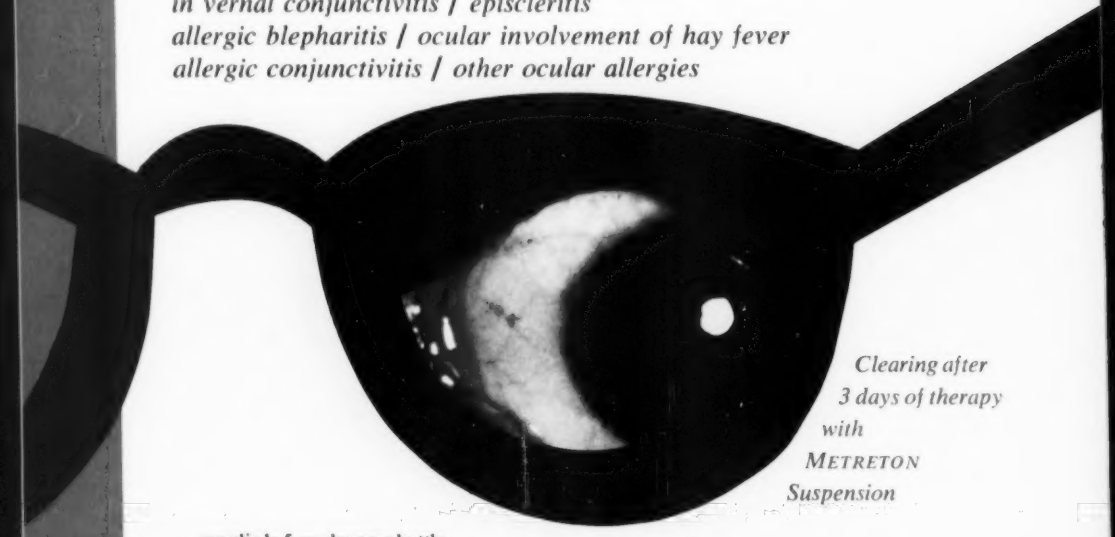

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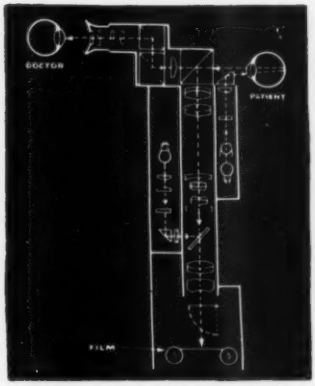

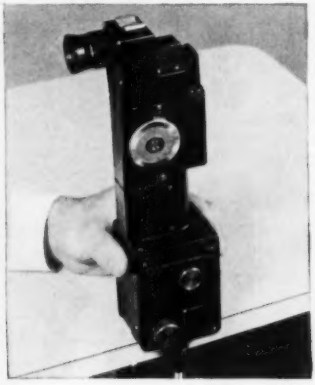

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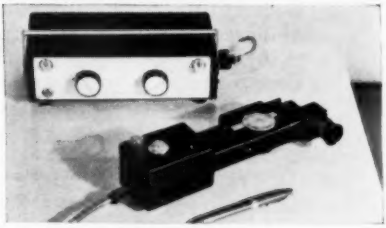

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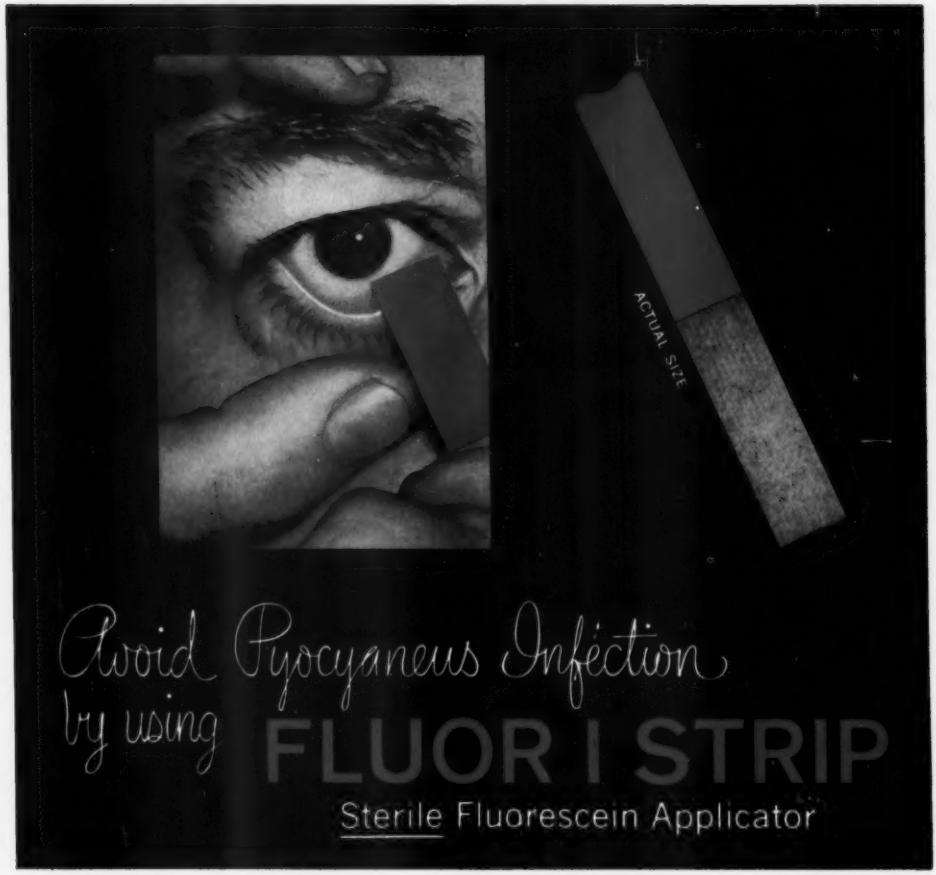

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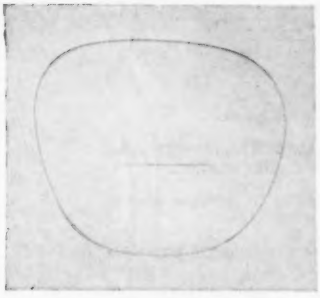

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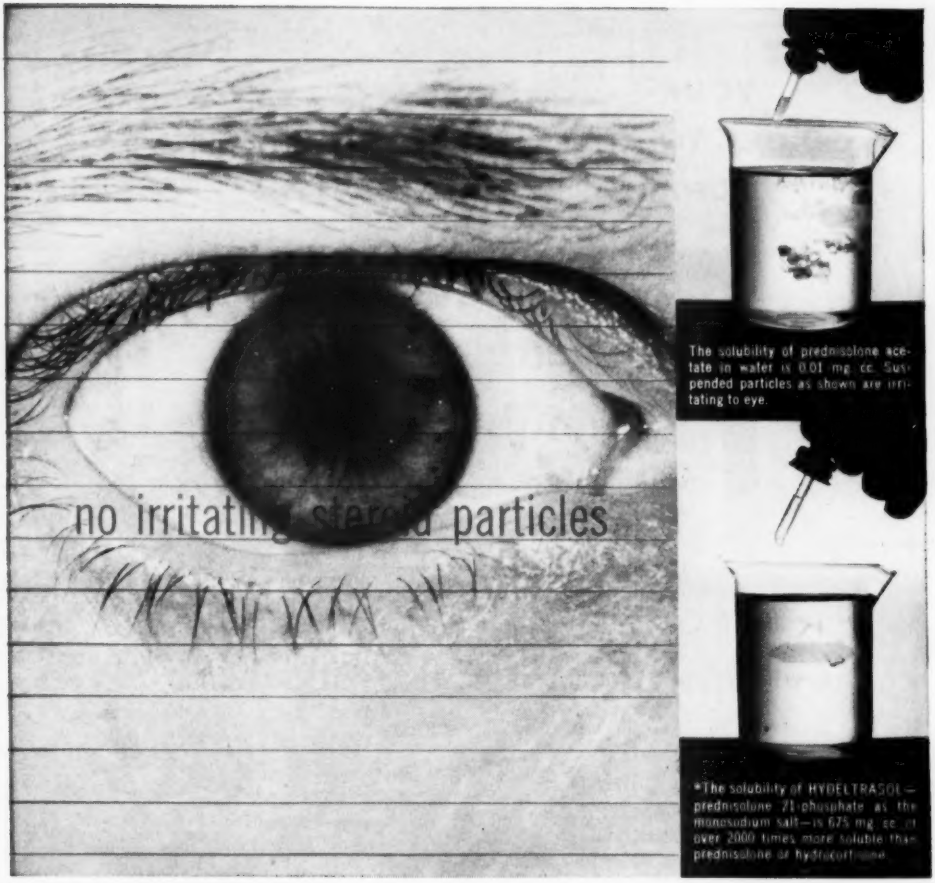
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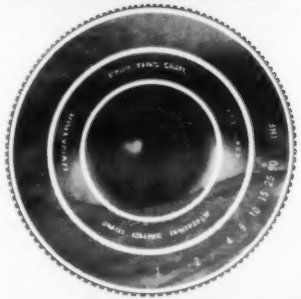

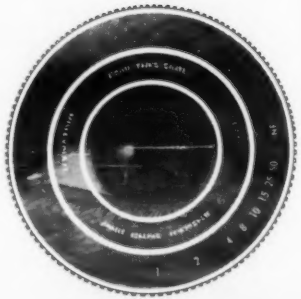

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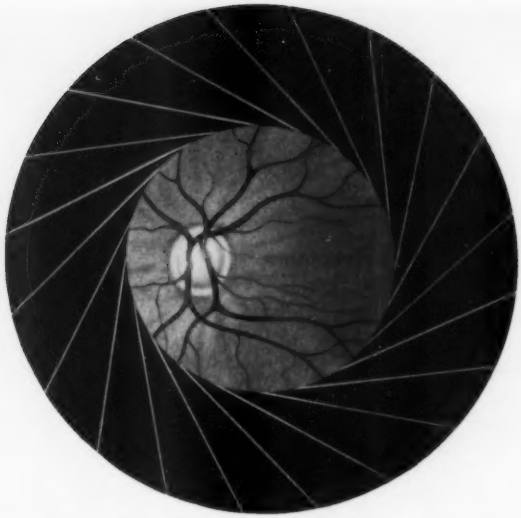

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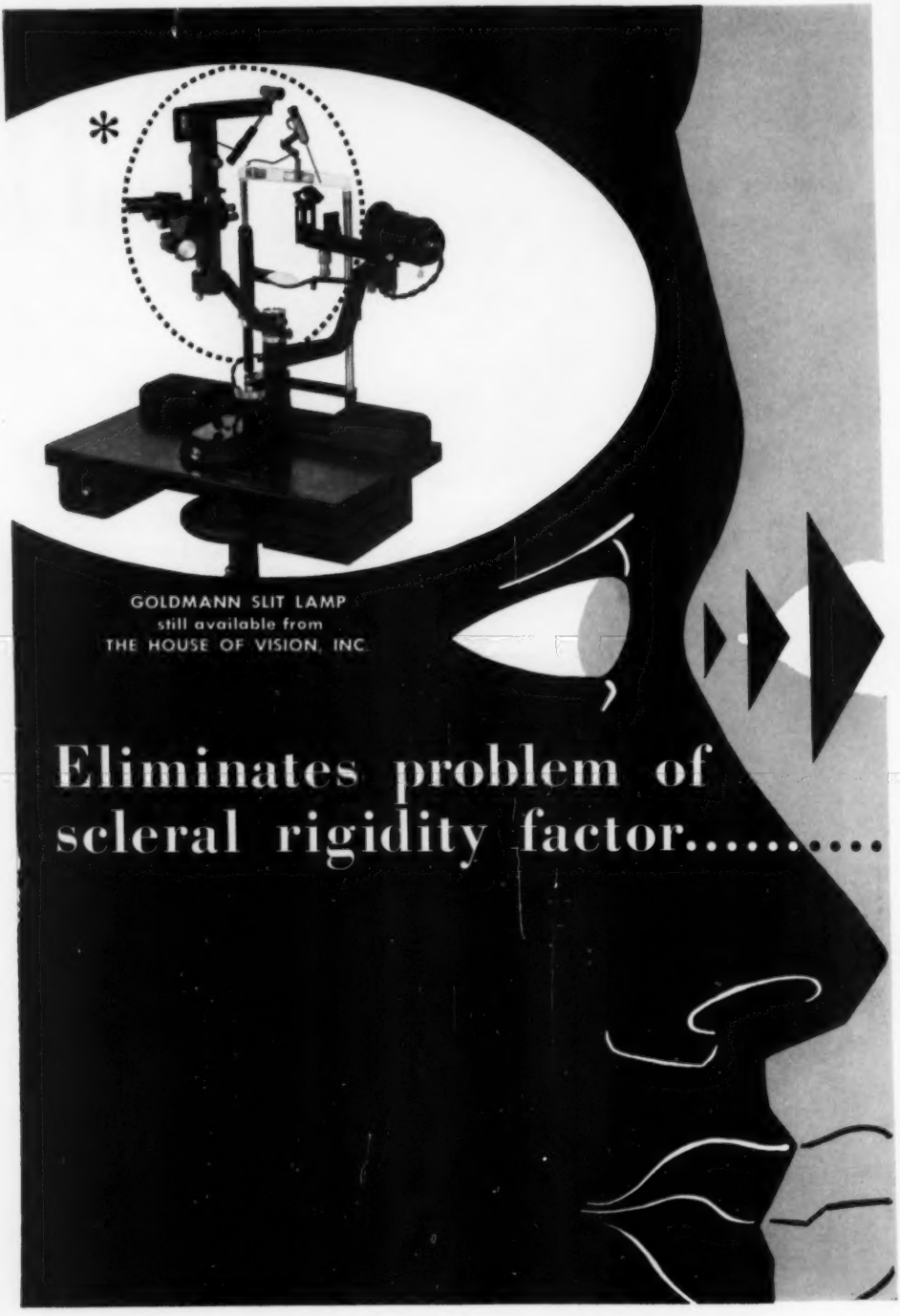
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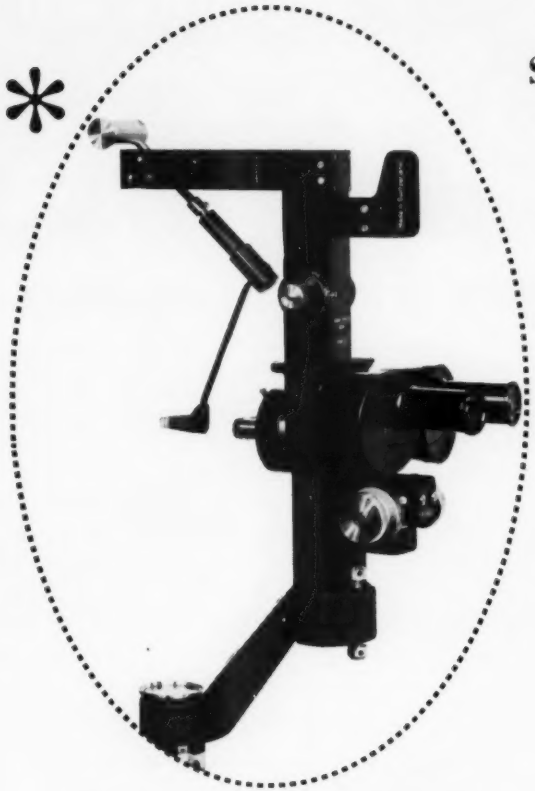

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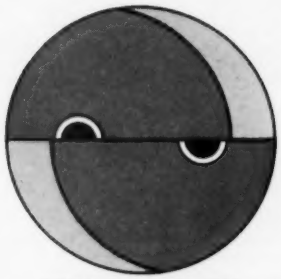

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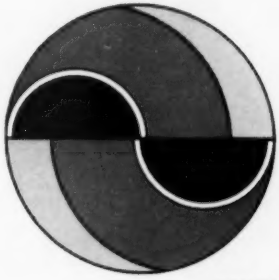

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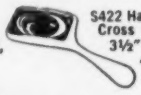
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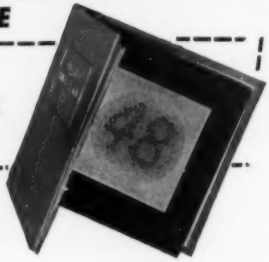

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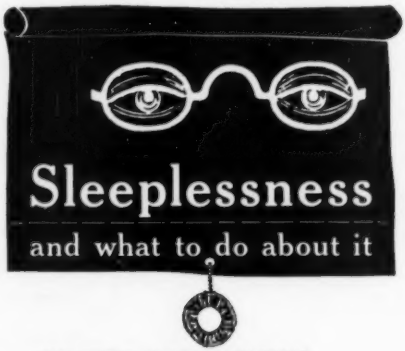

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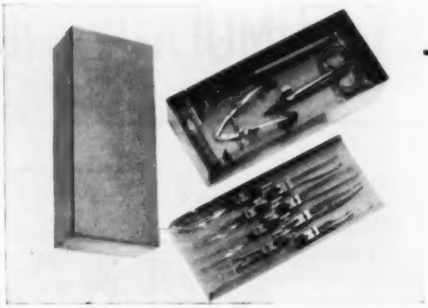

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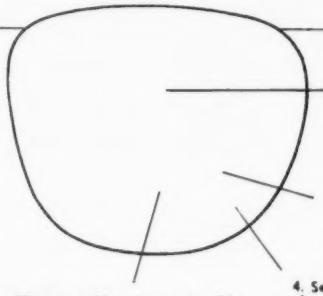

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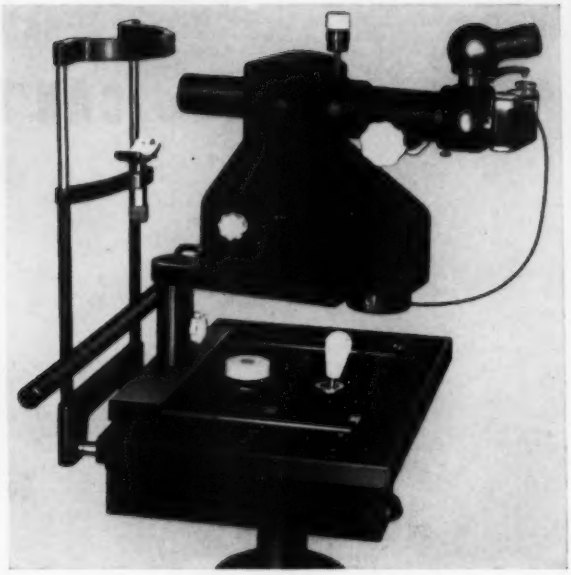

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Editorials

Eye Care and Prepayment Plans

The concept of prepaid medical care has met with marked approval as evidenced by the acceptance of ever-increasing individual insurance programs by the American people. Many of these are insurance policies by which individuals and employees are covered. Others in the nature of "fringe benefits" are enjoyed by groups, such as labor unions. A program embracing advantages of the latter to the American public was one of the last major endeavors of the late Edwin Forbes Tait, M.D., whose contributions were many in the scientific and socioeconomic fields of ophthalmology.

As a lasting tribute to him comes a new pamphlet from the National Medical Foundation for Eye Care on "Eye Care and Prepayment Plans," a field in which he was especially well versed because of many years of service on the Legislative Committee of the Pennsylvania State Medical Association.

In an ever-changing world, it behooves every ophthalmologist to acquaint himself with the introduction to this publication.

Introduction

American medicine is becoming more and more cognizant of and affected by the development of third-party payment plans for medical services, and physicians engaged in the practice of specialties, such as ophthalmology, are not excepted.

Until recent years, there have usually been only two persons involved in most medical services—the patient and his physician, with the patient paying the doctor directly for services received. Payment by third parties for medical services was limited to salaries or fees paid to physicians by national, state, and local governments, including the Armed Forces, and payments to physicians serving industrial patients in first aid or treating compensable conditions. Health and accident insurance companies ordinarily paid indemnity to the patient directly. Physical examinations for industry were and are also done, but this is a service primarily to the industry rather than to the patient.

The advent of prepaid medical care, even though on a "fee-for-service" basis, with the insurance organization paying the physician directly, as in Blue Shield, has created many problems for the medical profession. These problems are most complicated and acute in the case of health plans set up by industries, unions, and other groups, directed by laymen and served by physicians who are usually employed and discharged at the will of their employer.

Whether or not physicians approve of all of these developments, they are faced with them. If the process continues, as certainly seems likely, a large minority, if not a majority of the people in the United States will, within a few years, have some third party, governmental or private, paying the physician for many of his services to them.

The physician will always insist that the primary concern be the welfare of the patient, and any scheme for payment of medical services by other than the individual patient will be acceptable only if this principle is observed.

Physicians must not compromise or negotiate the basic principles which affect good patient care. However, proposals which refer only to payment for such care may be negotiated. The Principles of Ethics of the American Medical Association are for the protection of the patient and are concerned with economic factors only insofar as they may affect the patient's well-being.

In this report will be found a condensed history of the development of medical service plans, including those of industry, labor unions, and private corporations; a discussion of the position of organized medicine and that of the union health and welfare funds; a suggested pilot plan for ophthalmological services, and a discussion of this, all designed to acquaint the practicing ophthalmologist with these developments and with possible ways in which physicians can deal with them within the letter and spirit of the Principles of Ethics of the American Medical Association.

RALPH O. RYCHENER, M.D.
1720 Exchange Building
Memphis 3

The reader is referred to a Report of the Commission on Medical Care Plans, Part I: Findings, Conclusions, and Recommendations, Sept. 1958, American Medical Association.

Tonometer Tensions in the Newborn

CONRAD L. GILES, M.D., Ann Arbor, Mich.

There are many recordings of intraocular pressures of both normal and abnormal eyes, but a careful review of the literature reveals that the only previous recordings of tonometer tensions in the newborn were made by Brockhurst [1] on 59 *premature* infants. This paper will analyze the results of a study involving 32 *full-term* infants in whom the intraocular pressure was measured with a Schiøtz impression tonometer within one hour after birth.

Method of Study

A total of 110 newborns were seen no more than one hour after birth, and an attempt was made to obtain a tonometer tension. In only 32 cases out of this entire group was it possible to determine a tension which was considered to be truly reflective of the newborn's intraocular pressure.

Immediately after delivery the child was brought into the newborn nursery, cleaned, and wrapped in a blanket which restrained his hands. The head of the infant was held in place by a nurse, the lids gently opened, the eyes carefully examined externally and funduscopically before taking the tensions, and the tonometer was then placed on the cornea. The tonometer was reapplied two times, and readings were taken, averaged, and recorded. Each eye was examined daily after the procedure. Only those infants whose eyes rested in approximately the primary position and in whom three accurate readings could be obtained are included in this group of 32. Tetracaine (Pontocaine) 0.5% was used in only five instances, since it became apparent that the anesthetic drops affected the child more than the actual application of the tonometer.

It is both surprising and of interest that the main factor determining exclusion of cases from the series was not the inability of the child to hold his eyes still but rather was dependent on the size of the palpebral fissure. It was necessary to use the standard Schiøtz tonometer in this study, and because of the large size of the footplate many cases had to be excluded because of small palpebral fissures. Total uncooperation, cyanosis, and prolonged crying also played significant roles in the elimination of cases from the study. The relative cooperation of the newborn infant in the immediate postnatal period is quite striking, as is the change in his attitude in his second hour of life, when he becomes more aware of his surroundings and much less amenable to tonometry. A nipple stuffed with cotton served successfully as a "pacifier" in a number of instances.

None of the infants were anesthetized, although admittedly there were varying degrees of alertness in these newborns, depending mainly upon the anesthetic and preanesthetic medication used in the delivery. Seventeen (53%) of the infants were delivered with the use of caudal or saddle-block analgesia, while only eight (25%) of them were delivered under general anesthesia, usually a nitrous oxide and oxygen combination. The remaining seven (22%) were delivered with the use of self-administered trichloroethylene (Trilene), pudendal block, or no anesthesia whatever. Predelivery analgesics were used judiciously in all cases.

Results

The tonometer tensions of the 32 newborn infants are listed in Table 1. These

Submitted for publication Sept. 25, 1958.

From the Department of Ophthalmology, The University Hospital, The University of Michigan Medical School.

TABLE 1.—*Tonometer Tensions in Thirty-Two Newborn Infants*

Case No.	O. D.	O. S.	Case No.	O. D.	O. S.
1	23.8	20.1	17	18.5	20.1
2	13.1	12.0	18	23.8	21.9
3	21.9	25.8	19	20.1	21.9
4	25.8	25.8	20	25.8	25.8
5	23.8	21.9	21	17.0	18.5
6	25.8	25.8	22	21.9	20.1
7	23.8	21.9	23	25.8	25.8
8	28.0	25.8	24	25.8	21.9
9	18.5	17.0	25	30.4	28.0
10	30.4	18.5	26	20.1	18.5
11	21.9	21.9	27	21.9	25.8
12	20.1	25.8	28	20.1	21.9
13	15.6	18.5	29	25.8	18.5
14	15.6	17.0	30	25.8	28.0
15	25.8	30.4	31	25.8	25.8
16	25.8	28.0	32	21.9	15.6

tensions were found with the use of a 7.5 gm. weight on the standard Schiøtz tonometer. The upper limits of normal in the adult under similar circumstances is 25.8 mm. of mercury. The standard Schiøtz tonometer table from which these figures are derived is presented in Table 2.

In no case did the intraocular pressure exceed 30.4 mm. of mercury, and in only six cases, No. 8, 10, 15, 16, 25, and 30, was the generally accepted normal figure exceeded. No significant difference was noted in the intraocular pressure recordings of those infants who were delivered under general anesthesia or regional block. Instrument deliveries had no apparent effect on the tensions. No congenital ocular abnormalities were seen in any of the infants examined, and with the exception of retinal hemorrhages nothing unusual was found on funduscopic examination. The latter factor (i. e., retinal hemorrhages) did not seem to influence the recordings.

Each infant was carefully followed daily for three to seven days, depending on the day of discharge from the hospital, for the development of corneal ulceration. No untoward effects of the application of the tonometer were noted.

TABLE 2.—*Standard Schiøtz Tonometer Calibration Scale*

Tonometer Reading	Pressure (Mm. Hg), 7.5 Gm.
0.0	59.1
0.5	54.2
1.0	49.8
1.5	45.8
2.0	42.1
2.5	38.8
3.0	35.8
3.5	33.0
4.0	30.4
4.5	28.0
5.0	25.8
5.5	23.8
6.0	21.9
6.5	20.1
7.0	18.5
7.5	17.0
8.0	15.6
8.5	14.3
9.0	13.1

Comment

Before accepting the above figures as being absolute determinations, one must be aware of the limitations of this study. The first and most important of these limitations is the use of the standard tables devised by Friedenwald and recently revised by him in 1955. Sugar,[2] in his discussion of tonometry, notes that the impression tonometer as a measure of intraocular pressure is based largely on the impressibility of the tunics of the eye. This impressibility, or "ocular rigidity," of the adult eye has been adequately derived, but Friedenwald states,[3] "when using the standard Schiøtz chart . . . no consideration is being made of the difference between the newborn and adult ocular rigidity." It is certainly probable that some difference does exist between the rigidity of the newborn eye and that of the adult, and when we transpose the readings from the tonometer on the standard chart we are undoubtedly introducing an unknown amount of error.

Another more obvious limitation of this study is the method by which the tensions were obtained. Unlike the adult patient, who is able to seat himself comfortably in a reclining chair and fix at a distant but constant point while the tonometer tension is being taken, the newborn infant must be held in place and the tensions obtained under more or less "catch-as-catch-can" circumstances.

It is well known that variations in the intraocular pressure of the adult and infant can occur with straining or attempting to close the lids. In the case of the newborn infant this straining must play a part in false elevation of the intraocular pressure readings.

In spite of the aforementioned limitations and deviation from standard tonometry procedure, I feel that the figures presented represent a "practical" estimation of the intraocular pressure of the newborn. The figures bear out a heretofore theoretical premise that the intraocular pressure of the normal newborn parallels that of the adult.

Summary and Conclusions

The technique of study and findings of 32 impression tonometer tensions in newborn infants obtained one hour after birth are presented. With use of the standard adult tables as a reference, it appears that the intraocular pressure of the newborn approaches the upper limits of adult normality. The limitations of interpretation of such tonometer tensions are briefly discussed.

Dr. George Sayre, Chief of Obstetrics, and his staff, and Miss Marguerite Lander, Chief of Nursing, and her staff at Beyer Memorial Hospital, Ypsilanti, Mich. cooperated in this study.

University Hospital.

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The Rate of Aqueous Flow in Human Eyes With and Without Senile Cataract

A Study by Means of the Suction-Cup Method

ERIK LINNÉR, M.D., Gothenburg, Sweden

The metabolism of the lens under normal and pathological conditions has been studied extensively, and various factors which produce opacities of the lens are known. The changes leading to senile cataract in human beings are not understood, however (for review of the literature see Bellows,[2] Friedenwald et al.,[6] and Nordmann [15]).

The lens does not have its own blood supply and is, for its nutrition, dependent on the aqueous humor. It seems reasonable to assume that changes in flow or composition of the aqueous humor can produce changes in the normal metabolism of the lens, leading to opacities. An investigation of the rate of aqueous flow with a comparison between normal human eyes and eyes with cataract would, therefore, be of interest.

Different methods for determining the rate of aqueous flow in human eyes have been developed. The tonographic method shows an uncertainty in the estimate of aqueous flow, especially at normal intraocular pressure when the outflow pressure is low. The fluorometric method according to Goldmann is difficult to use with accuracy in eyes with cataract owing to the fact that the determinations of the fluorescein concentration in aqueous humor must be made against a gray background instead of a black one.

Recently a new method—the suction-cup method—was developed in Gothenburg. This method was considered to be the most suitable for the purpose of the present study and was therefore chosen for a comparative study of the rate of aqueous flow in human eyes without cataract and in eyes with senile cataract. Although this method does not give accurate absolute values, it can be used for comparative purposes. The error of the method is of the order of magnitude to allow determination of moderate changes in aqueous flow.

In additional experiments the effect of a vasodilating agent was examined.

Material

The group of human beings without cataract consisted of 78 persons. Forty-five patients in this group were selected from the outpatient department. The patients showed smaller refractive errors or external eye diseases. Some of the older ones showed senile macular degeneration. Their age varied between 16 and 89 years.

By slit-lamp examination the lenses of the older patients were found to have small peripheral opacities, as normally seen at this age. Thirty-three healthy student nurses between 20 and 30 years of age were also included in this group.

A separate group of 37 patients showing senile cataract in both eyes, the stages of the cataract varying from early to mature, were chosen for this study. Patients who showed other diseases of the eye as well were not included in this study.

Submitted for publication July 30, 1958.

Presented in part before the Swedish Ophthalmological Society, June 7, 1958.

This study was supported by a grant from the Swedish Medical Research Council.

From the Department of Ophthalmology, Sahlgren's Hospital, University of Gothenburg; Prof. Bengt Rosengren, Head.

Dr. T. Lindqvist gave information about Hexanicit and its effect on patients with different vascular disorders. Hexanicit was supplied by Bofors Nobelkrut Co., Sweden.

All patients showing an intraocular pressure of 24 mm. Hg or above this level, according to Friedenwald's new tables (1955),[4] were disregarded. No cases of glaucoma were accepted.

A nicotinic acid preparation, Hexanicit, was also given to 17 student nurses included in the group without cataract and to 14 patients with senile cataract. In both groups the subjects were chosen at random. Two tablets containing 0.2 gm. were given three times daily during two days before the examination.

Method

In the suction-cup method, a suction cup was placed perilimbally upon the eye. At an adequate vacuum below atmospheric pressure in the suction cup, the contact surface exerted a pressure against the eye which was great enough to compress the conjunctival and episcleral veins, thus blocking the outflow channels for aqueous humor. This blockade resulted in an increase of the intraocular pressure produced by an accumulation of aqueous humor in the eye. The method was described by Rosengren.[18-20] This method was then carefully studied by Ericson,[3] who found it useful for comparative purposes.

The standard procedure described by Ericson was used in this study. The suction cup, made of plastic material, had a contact surface with an inner diameter of 12.0 mm. and an outer diameter of 20.0 mm. The radius of curvature of the contact surface was 12.7 mm.*

* The suction cup is manufactured by AB Vacuum-Extractor, Drottninggaton 13, Gothenburg, Sweden.

TABLE 1.—*The Intraocular Pressure and the Rate of Aqueous Flow in Human Eyes Without Cataract*

		Age, Yr.			
		16-89	16-29	30-59	60-89
P_o*	n	78	35	25	18
	$m\pm e$	16.7±0.27	16.1±0.39	17.1±0.44	17.4±0.61
	s	2.39	2.31	2.19	2.60
F	n	78	35	25	18
	$m\pm e$	12.3±0.32	13.4±0.31	11.6±0.71	11.1±0.60
	s	2.82	1.86	3.56	2.54

* Symbols: P_o=intraocular pressure in mm. Hg; F=rate of aqueous flow in cubic millimeters per 15 min.; n=no. of cases; m=arithmetic mean; e=standard error of the mean; s=standard deviation.

All determinations were made between 10 a. m. and 2 p. m. The patient was examined in the recumbent position, and Venoxinate (Novesin; Wanderer, Berne) was used as a topical anesthetic. After the intraocular pressure had been measured with a certified Haag-Streit tonometer, the suction cup was placed upon the eye for a period of 15 minutes. (In a few additional measurements the time was limited to five minutes.) Immediately after removal of the suction cup the intraocular pressure was remeasured. The increase in pressure during this period was then used for calculating the increase in volume, with use of Friedenwald's [4] new tables of 1955. The amount of aqueous humor produced in this period of time was then estimated from the accumulated volume in the eye. The value was assumed to be representative for the rate of aqueous flow and was expressed as cubic millimeters per 15 minutes. No corrections were introduced.

In order to increase the accuracy of the method both eyes of each patient were stud-

TABLE 2.—*The Difference in Intraocular Pressure and Rate of Aqueous Flow Between Right and Left Eye in Cases Without Cataract*

	Intraocular Pressure	Rate of Aqueous flow			
	16-89 Yr.	16-89 Yr.	16-29 Yr.	30-59 Yr.	60-89 Yr.
n*	78	78	35	25	18
$m\pm e$	+0.074±0.081	+0.47±0.30	+0.47±0.36	+0.57±0.43	+0.34±0.58
s	0.72	2.69	2.16	2.13	2.44

* Symbols: n=no. of cases; m=arithmetic mean; e=standard error of the mean; s=standard deviation.

TABLE 3.—*Intraocular Pressure and Rate of Aqueous Flow in Persons Without Cataract*

		Age, Yr.					
		16-29		30-59		60-89	
		P_o*	F	P_o	F	P_o	F
Males	n			7	7	11	11
	$m \pm e$			17.1±0.96	13.0±1.02	17.3±0.81	10.9±0.85
	s			2.55	2.70	2.68	2.81
Females	n	34	34	18	18	7	7
	$m \pm e$	16.1±0.40	13.4±0.32	17.1±0.50	11.0±0.89	17.7±1.01	11.5±0.84
	s	2.35	1.88	2.11	3.77	2.67	2.21

* Symbols: P_o=intraocular pressure in mm. Hg; F=rate of aqueous flow in cubic millimeters per 15 min.; n=no. of cases; m=arithmetic; e=standard error of the mean; s=standard deviation.

ied. The examination was performed first on the right eye and after an interval of half an hour on the left eye. The mean of the two eyes was used as a representative value for each subject.

Results

The findings of the group without cataract are demonstrated in Tables 1, 2, and 3 and in Figures 1 and 2. The intraocular pressure, 16.7 mm. Hg, was similar to that found in other studies with use of a certified tonometer and Friedenwald's new tables (1955). The differences observed between the different age groups, between the right and the left eye, or between male and female were numerically small and not significant.

The rate of aqueous flow was 12.3 cu. mm/15 minutes in the whole group (16-89 years). In the youngest group (16-29 years) a value of 13.4 cu. mm/15 minutes was found. This value is significantly higher than 11.6 found in the intermediate age

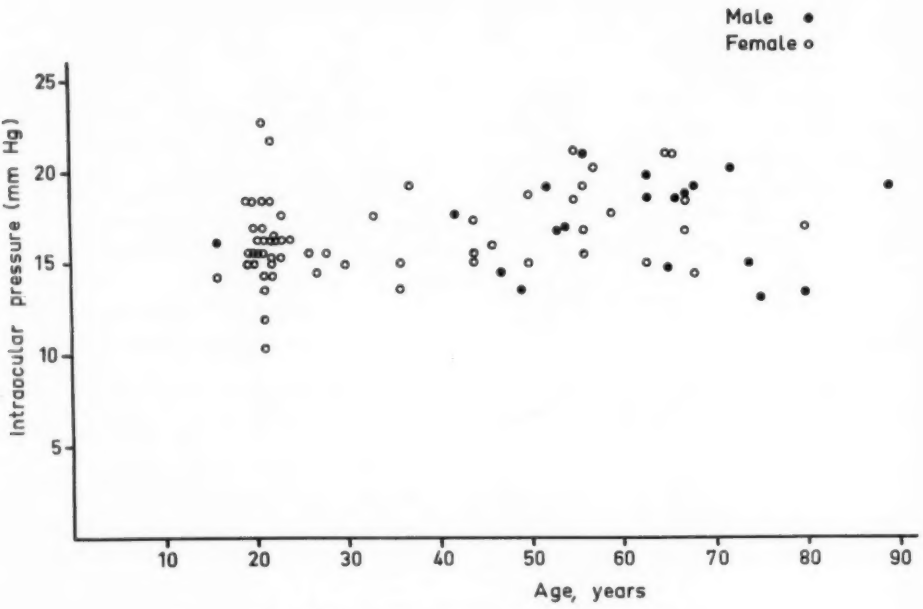

Fig. 1.—The Relationship Between Age and Intraocular Pressure.

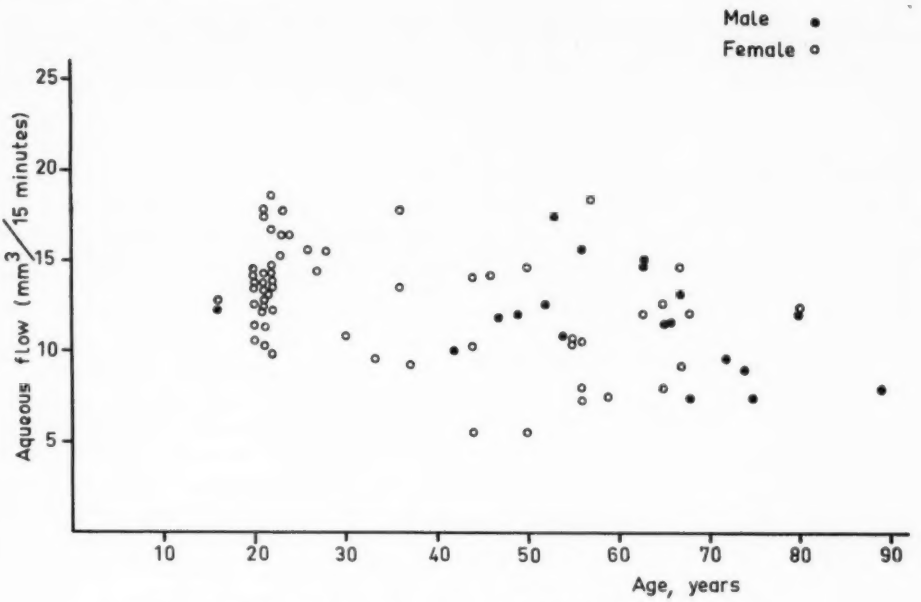

Fig. 2.—Relationship Between Age and Aqueous Flow.

group (30-59 years) ($0.01<P<0.05$). On the other hand, a numerically small and not significant difference was demonstrated between the intermediate group (30-59 years) and the oldest one (60-89 years). These findings indicate that a decrease in the rate of aqueous flow takes place before 60 years of age down to a rate which in this material is not further diminished at a higher age. The standard deviation was found to be significantly greater in the intermediate than in the youngest group ($0.001<P<0.01$), constituting a further indication of the change in aqueous flow during this age (30-59 years). The tendency toward lower aqueous flow at higher age therefore cannot be represented by a straight regression line. A tendency toward a lower value of aqueous flow at a higher age was demonstrated by Ericson.[3] The age must therefore be taken into account by comparison between different groups of persons. The value 13.4 in the youngest group is somewhat higher than the value found by Ericson in a separate group of student nurses. However, the intraocular pressure determined by Ericson was based on two tonometric readings causing a massaging effect. This effect tends to give too low an estimate of aqueous flow.

The difference between the right and the left eye as well as between male and female was found to be numerically small and not significant (Tables 2 and 3).

In the group of patients with senile cataract the intraocular pressure was 16.7 mm. Hg, as compared to 17.4 in the corresponding age group of patients without cataract (60-89 years). This difference is not significant. The rate of aqueous flow was found to be lower in the group with cataract, 8.6 cu. mm/15 minutes, than in the group without cataract, 11.1 cu. mm/15 minutes, and this difference is highly significant ($P<0.001$). The standard deviations of the two groups were found to be of the same order of magnitude, and the differences were not significant (Tables 1 and 4). In the group of patients with senile cataract the difference between the right and the left eye was numerically small and not significant (Table 5). The average age in the group with cataract was 69 years, as com-

TABLE 4.—*Intraocular Pressure and Rate of Aqueous Flow in Human Eyes with Senile Cataract*

	P_o*	F	P_o Ratio of Mat/Inc.	F Ratio of Mat/Inc.
n	37	37	16	16
$m \pm \varepsilon$	16.7±0.42	8.6±0.41	1.00±0.026	1.04±0.12
s	2.53	2.47	0.103	0.49

* Symbols: P_o=intraocular pressure in mm. Hg; F=rate of aqueous flow cubic millimeters per 15 min.; Mat=mature cataract; Inc.=incipient cataract; *n*=no. of cases; *m*=arithmetic mean; ε=standard error of the mean; *s*=standard deviation.

TABLE 5.—*Difference in Intraocular Pressure and Rate of Aqueous Flow Between Right and Left Eye in Cases with Senile Cataract*

	P_o*	F
n	37	37
$m \pm \varepsilon$	−0.12±0.22	+1.16±0.54
s	1.33	3.26

* Symbols: P_o=intraocular pressure in mm. Hg; F=rate of aqueous flow cubic millimeters per 15 min.; *n*=no. of cases; *m*=arithmetic mean; ε=standard error of the mean; *s*=standard deviation.

pared to 70 years in the control group without cataract.

In 16 patients with senile cataract the two eyes showed a marked difference between the stages of their cataracts, and so the cataract of one eye was mature or close to maturity while that of the second eye was incipient. Neither the intraocular pressure nor the aqueous flow values, calculated as ratios between the eye with mature and the eye with incipient cataract, deviated significantly from unity (Table 4).

In order to investigate the possibility of producing an increase in the rate of aqueous flow, the effect of a vasodilating agent, Hexanicit, was examined in a preliminary study. Tables 6 and 7 demonstrate the effect of this treatment on 17 normal student nurses and 14 patients with senile cataract. In both groups the subjects were chosen at random. The intraocular pressure did not show any significant change in either group; the differences are numerically small as compared to the standard deviation. The rate of aqueous flow was found to increase during treatment with Hexanicit. In the normal group the increase from 13.6 to 14.5 cu. mm/15 minutes was significant if the results were calculated as ratios between the values obtained during and before the treatment ($0.01 < P < 0.05$). The change was not found to be significant if calculated as dif-

TABLE 6.—*Effect of Hexanicit on Aqueous Humor Dynamics in Normal Human Eyes*

	Before Treatment (I)		During Hexanicit (II)		Ratio of II/I	Difference II − I
	P_o*	F	P_o	F	F	F
n	17	17	17	17	17	17
$m \pm \varepsilon$	16.3±0.53	13.6±0.39	15.8±0.36	14.5±0.40	1.07±0.034	+0.87±0.45
s	2.20	1.59	1.47	1.63	0.14	1.87

* Symbols: P_o=intraocular pressure in mm. Hg; F=rate of aqueous flow in cubic millimeters per 15 min.; *n*=no. of cases; *m*=arithmetic mean; ε=standard error of the mean; *s*=standard deviation.

TABLE 7.—*Effect of Hexanicit on Aqueous Humor Dynamics in Human Eyes with Senile Cataract*

	Before Treatment (I)		During Hexanicit (II)		Ratio of II/I	Difference II − I
	P_o*	F	P_o	F	F	F
n	14	14	14	14	14	14
$m \pm \varepsilon$	17.3±0.80	9.2±0.47	17.0±0.81	10.3±0.62	1.11±0.039	+1.02±0.35
s	3.00	1.75	3.02	2.34	0.15	1.33

* Symbols: P_o=intraocular pressure in mm. Hg; F=rate of aqueous flow in cubic millimeters 15 min.; *n*=no. of cases; *m*=arithmetic mean; ε=standard error of the mean; *s*=standard deviation.

ferences ($0.05<P<0.10$). In the group of patients with senile cataract the increase from 9.2 to 10.3 cu. mm/15 minutes was significant ($0.01<P<0.05$) with both methods of calculation.

During the period of 15 minutes when the suction cup is placed upon the eye, the rate of aqueous flow gradually decreases, as demonstrated by Ericson.[3] He found that the rate of aqueous flow estimated during five minutes was 50% of that found during 15 minutes.

In order to study whether cataractous eyes treated with Hexanicit would behave in a similar way, an additional examination was performed on seven of these patients, with the suction cup placed upon the eye five minutes only. In this group the average rate of aqueous flow during 15 minutes was found to be 8.4 cu. mm. and that during 5 minutes, 3.5 cu. mm. The estimate calculated as a ratio for each subject was 46% during 5 minutes of that found during 15 minutes, which is in good agreement with the results found by Ericson.

Comment

The first problem to be considered is how far the figures obtained by means of the suction-cup method would give a correct reflection of the real rate of aqueous flow. There is good evidence that the figures are representative as long as they are used for comparative purposes. According to Ericson, the decrease in rate of aqueous flow during the suction is probably caused in large part by the increasing pressure. This question was discussed in detail by Ericson. Among other things, he found that acetazolamide caused a reduction in aqueous flow of more than 50%. This figure goes in the same direction but is somewhat higher than that found by other methods. The effect of prednisolone was studied by using the suction-cup method and tonography. The results obtained by these two methods were in good agreement (Linnér [13]).

A change in scleral rigidity would influence the results obtained by the suction-cup method. Miller, Keskey, and Becker [14] measured the intraocular pressure in patients with cataract with use of a tonometer with various weights and the Goldmann aplanation apparatus. Their results "revealed the scleral rigidity to be within the normal limits seen in a general clinical population."

The figures in the present study were therefore accepted as representative of the rate of aqueous flow, and it was assumed that these values should vary in the same way as the absolute values of aqueous flow.

On this assumption, this study demonstrates that the rate of aqueous flow was reduced in patients with senile cataract as compared to persons of the same age without cataract. In a previous study Kronfeld [8] did not report any change in aqueous flow of early cataracts as determined by tonography. Lee and Trotter [10] examined the rate of aqueous flow by means of tonography in 142 cataractous eyes before surgery. They found an average value of 1.57 cu. mm. per minute. This figure is lower than the value of 2.4 cu. mm. per minute obtained in normal eyes by Grant from the same laboratory using the same technique.[6]

The question is whether the reduction of aqueous flow in cataractous eyes started at about the same time as the cataract or prior to its development. The fact that no significant difference in aqueous flow was found between different stages of cataract seems to indicate that the reduction in flow might be already finished when the cataract is in an incipient stage and maybe even earlier.

No cataractous changes could so far be related to a chronic use of acetazolamide.[1, 7,9,21] This experience seems to indicate that the aqueous flow can be reduced at least during a few years before cataractous changes of the lens start to become visible. The conditions of the cataractous eyes and of the eyes treated with acetazolamide are not, however, necessarily compatible, even if the rate of aqueous flow is reduced in both cases.

In a previous study of patients with senile cataract, the rate of plasma flow through the ciliary processes was measured by means of ascorbic acid as test substance (Linnér [12]). The results indicated a reduction of plasma flow in eyes with senile cataract as compared to eyes without cataract. There was at that time no evidence that the rate of aqueous flow was reduced in cataractous eyes.

If the reduction in aqueous flow demonstrated in the present study is taken into account, the rate of transfer of ascorbic acid into the eye must be lower than previously assumed in order to be compatible with the reduced concentration of ascorbic acid in aqueous humor from cataractous eyes. Assuming that the rate of transfer of ascorbic acid into the eye reflects the plasma flow, the latter would also be further reduced. The magnitude of this reduction cannot be accurately estimated from the experimental data available at the moment.

Purcell, Lerner, and Kinsey [17] determined the concentration of ascorbic acid in aqueous humor and plasma from seven patients with and three without cataract. In these cases no significant difference was found in the ratio of concentration in aqueous humor to concentration in plasma. An accurate determination of the concentration of ascorbic acid in plasma is, however, difficult at a low ascorbic acid level.

Many investigations have been undertaken with the purpose of finding a substance which could restore the transparency of the lens or at least stop or delay the progress of the opacities. The problems concerned with medical therapy were recently discussed by Nordmann.[15,16] Different agents producing a vasodilation, such as ethyl morphine hydrochloride (Dionin) and iodine, have been tried. The effect of immunological and hormonal factors was also examined. In order to substitute for possible deficiencies, varying substances, such as vitamins, were given. Conclusive evidence of an effective medical therapy of cataract, however, has not yet been reported.

As a result of the present study it seems reasonable to assume a relationship between the senile cataract and the reduction in rate of plasma flow through the ciliary processes and in aqueous flow. It may be pointed out that it is not possible to evaluate at this moment how far a reduction in aqueous flow plays an essential role in the development of cataract. Other pathological changes in eyes with senile cataract cannot, of course, be excluded.

An attempt to increase the rate of plasma flow was fairly obvious in order to see if an increase in the rate of aqueous flow could thereby be produced. As a suitable agent with a moderate but prolonged vasodilating effect a nicotinic acid preparation, Hexanicit, was chosen. According to Lindquist,[11] the effect on different vascular disorders was favorable.

The increase in rate of aqueous flow produced by Hexanicit seems to open a way to normalize the reduced aqueous flow in cataractous eyes, at least to some extent.

Whether a long-term administration of Hexanicit can be used as a medical therapy in order to stop or delay the progress of lens opacities cannot be judged from this study. A definite conclusion concerning the possible use of this and similar drugs will depend upon further investigations over a long period of time.

Summary

With use of the suction-cup method the rate of aqueous flow was measured in human eyes with and without senile cataract. The aqueous flow was found to diminish at a higher age and to be significantly lower in eyes with senile cataract than in eyes without cataract.

The effect of a vasodilating drug was studied. An increase in the rate of aqueous flow was found to take place during this treatment.

Department of Ophthalmology, University of Gothenburg.

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Light Coagulation with Indirect Ophthalmoscopy

ROBERT J. BROCKHURST, M.D.; ERNST WOLF, Ph.D., and C. L. SCHEPENS, M.D., Boston

Chorioretinal burns due to exposure of the retina to direct sunlight have been recognized for many years as the cause of eclipse blindness. In 1916, Verhoeff and Bell analyzed the physical principles of this phenomenon and performed animal experiments wherein they were able to produce such burns.[1] In 1949, Meyer-Schwickerath used sunlight to cause chorioretinal burns to close retinal tears.[2] However, because of difficulties resulting from inclement weather and seasonal changes in the light intensity of the sun, he was prompted to devise a carbon-arc source of light, with a brightness of 100,000 to 200,000 stilb, for producing chorioretinal burns.[3,4] This instrument utilizes a direct ophthalmoscopy principle in order that the operator may observe the fundus during application of the high-intensity light. Meyer-Schwickerath has used this technique successfully in the treatment of posterior fundus lesions, such as macular holes, tumors, and new-formed vessels. In addition, he has treated more peripheral retinal breaks but states that light coagulation is effective only to the limits of direct ophthalmoscopy.

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From the Retina Foundation, Department of Ophthalmology of the Massachusetts Eye and Ear Infirmary and Harvard Medical School.

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Histological sections were made at the Eye Pathology Laboratory, Massachusetts Eye and Ear Infirmary. Photomicrographs were taken by Mr. David Feigenbaum, Harvard Medical School. Illustrations were drawn by Mr. William Stenstrom, Retina Foundation.

In view of the many advantages of indirect ophthalmoscopy over direct ophthalmoscopy in locating fundus lesions,[5,6] especially in the peripheral portions of the fundus, it seemed desirable to develop an instrument for light coagulation utilizing indirect ophthalmoscopy. Such an instrument would not only permit more rapid and accurate localization of lesions to be treated but would also permit more adequate treatment of lesions located anterior to the equator. This is the area where most retinal breaks are found and where a nonsurgical approach to the treatment of retinal breaks without detachment is most often applicable. In addition, because carbon-arc light sources require extremely high amperage and are somewhat erratic in their performance, it was felt that a different source of light should be tried.

In this paper we wish to describe a new type of instrument for light coagulation * which incorporates a mercury-vapor-arc light and indirect ophthalmoscopic control of the burning light (Fig. 1). The light source, *A*, is an Osram HBO 107 mercury-vapor-arc lamp which operates on direct current, 50 volts at 5 amp., and has a brightness of 100,000 stilb. The light from the lamp passes through collimating lenses, *B*, then through a shutter, *C*, and is reflected by a semitransparent mirror which reflects 85% of the light at *D* into the subject's eye, *E*. The shutter has four small holes arranged in a square which provide sufficient light for focusing and fundus observation while the shutter is closed; this amount of light lacks sufficient energy to cause coagulation of the retina.

* The instrument described in this paper was built by American Optical Company, Southbridge, Mass.

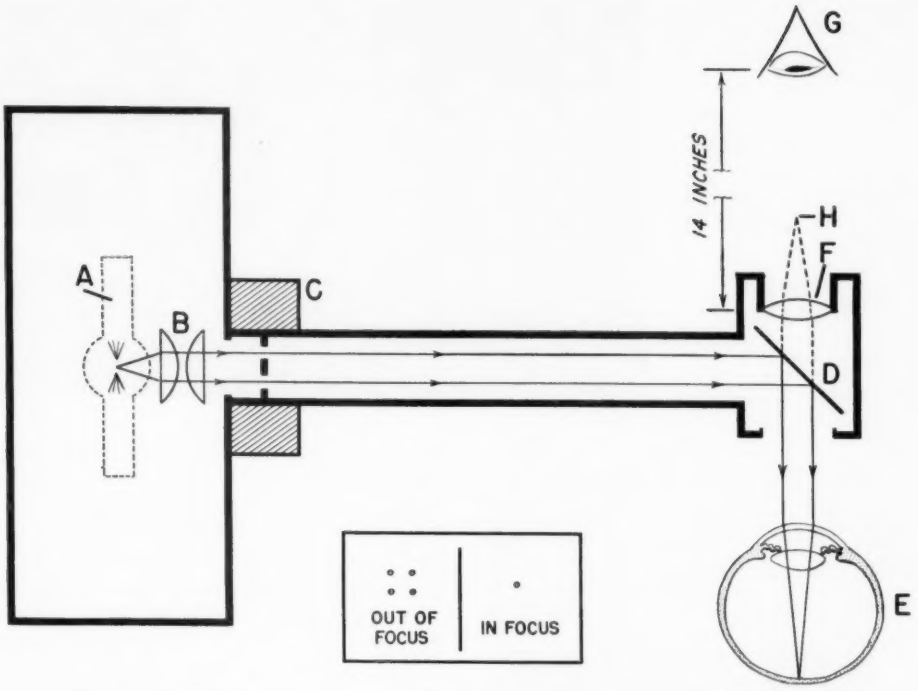

Fig. 1.—Diagram of mercury-vapor-arc lamp and optics of instrument: *A*, Osram mercury lamp; *B*, collimating lenses; *C*, shutter; *D*, mirror; *E*, subject's eye; *F*, +20 D. condensing lens; *G*, observer; *H*, inverted image of subject's fundus.

A +20 D. condensing lens for indirect ophthalmoscopy is incorporated into the instrument at *F*, and the observer, *G*, views the real inverted image, *H*, of the fundus.

In order to obtain a binocular view of the image, it is only necessary for the operator to wear a binocular indirect ophthalmoscope. Since light from the mercury-vapor lamp passes through the small holes of the shutter and thus illuminates the fundus, the illuminating light of the binocular indirect ophthalmoscope is not used.

In order to obtain chorioretinal burns, it is necessary that the light be brought to a sharp focus on the choroid and retina. In emmetropia the parallel light passing through the four holes in the closed shutter is reflected into the subject's eye by the semitransparent mirror and brought to a sharp focus, so that one small point of light is seen in the fundus. In spherical ametropia, however, the parallel light passing through the four holes in the closed shutter is not brought to a focus. Instead, four separate points of light are seen (inset of Fig. 1). Focusing on the retina is then accomplished by changing the distance between the mercury-vapor lamp and the collimating lenses by means of a micrometer screw until the four points merge. When the light is accurately focused and directed at the area of the fundus to be treated, the shutter is opened to expose the fundus to the full intensity of the mercury-vapor lamp.

Experimental chorioretinal burns have been produced in pigmented adult rabbits and guinea pigs with this apparatus (Fig. 2). Maximal mydriasis is necessary since the pupillary aperture limits the amount of light energy reaching the retina and choroid. In order to control the placement and intensity of the burn, it is necessary to an-

Fig. 2.—Operator with binocular indirect ophthalmoscope exposing rabbit eye to light coagulator.

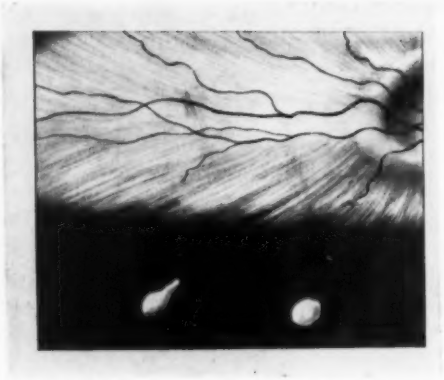

Fig. 3.—Fundus drawing showing appearance of acute chorioretinal burns immediately after exposure to high-intensity light.

esthetize the animals with intravenous pentobarbital sodium. Acute retinal edema with a surrounding halo of choroidal hyperemia is produced with exposures of 0.10 to 0.50 seconds (Fig. 3); the diameter of single burns varies from 0.1 to 0.2 mm. Larger areas can be obtained by longer exposures, but this also results in excessive coagulation necrosis of the retina. Figure 4 shows a section of a mild burn of the rabbit eye two days after exposure. Only slight edema of the nerve fiber layer of the retina is present, whereas considerable disorganization of the external nuclear layer and rods and cones is observed. This results from the fact that heat is produced where the

Fig. 4.—Histological section of chorioretinal burn in rabbit eye two days after exposure.

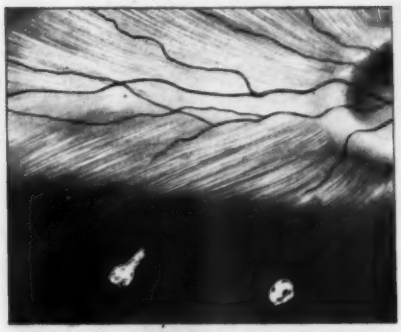

Fig. 5.—Fundus drawing showing healed chorioretinal burns in rabbit eye.

light is absorbed, namely, in the pigment epithelium and choroid. The choroidal vessels are markedly dilated. After five to seven days, pigmentation begins to appear, and finally the lesion resembles a typical chorioretinal scar as seen in chorioretinitis due to diathermy applications (Fig. 5). Histologically the area then shows a well-demarcated chorioretinal adhesion (Fig. 6).

Attempts have been made to produce chorioretinal burns in human patients whose eyes were to be enucleated because of the presence of an intraocular neoplasm. Since the focal length of the human eye is more than two times that of the rabbit eye, the intensity of the light reaching the human retina is less than one-half of that which reaches the rabbit retina. The present equipment has produced a chorioretinal burn, but a fairly long exposure to the light was necessary. Experimental work is now in progress to improve the light output of the instrument so that effective and rapid burns may be obtained in human eyes.

Light coagulation of the human retina and choroid offers a simple and effective method of treatment of retinal lesions such as small tumors; retinal breaks without detachment; intensification of diathermic choroiditis after reattachment of the retina; destruction of new-formed vessels, as in Eale's disease, and possibly destruction of small foci of chorioretinitis. We feel that a convenient device which utilizes safe levels of power and indirect ophthalmoscopy will increase the usefulness of light coagulation. Now that such an instrument for experimental use has been built and tested, further modifications and refinements are under way to adapt it for clinical use.

Summary

A new type of instrument is described for causing chorioretinal burns in the living eye. It incorporates a mercury-vapor-arc lamp and stereoscopic indirect ophthalmoscopy for observation of the fundus. Animal experiments were performed and histological

Fig. 6.—Healed chorioretinal adhesion in rabbit eye two months after exposure.

studies were made of the chorioretinal burns obtained. Further modifications of the instrument are now under way so that an effective clinical device may be perfected.

99 W. Cedar St. (14).

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Visual Acuity in Normal and Amblyopic Patients Under Reduced Illumination

I. Behavior of Visual Acuity With and Without Neutral Density Filter

GUNTER K. von NOORDEN, M.D., and HERMANN M. BURIAN, M.D., Iowa City

In 1921, a study was reported by Ammann,[1] in which the visual acuity of office patients was measured under ordinary conditions and with dark glasses, which, as the author stated, were of sufficient density to decrease the visual acuity for several lines on a reading chart. He found that the ratio between normal visual acuity and visual acuity with filter was as 1:0.3 to 1:0.5 in a group of normal patients. A group of amblyopic patients was examined in a similar manner, and the astonishing observation was made by Ammann that these eyes were not infrequently able to read the same line on the chart with and without filter.

Our recent electro-ophthalmographic observations[2] about the extraordinary capacities of eyes with squint amblyopia under reduced illumination stimulated us to do a similar study, not only because Ammann's work has to our knowledge never been repeated or confirmed but also because his findings, if confirmed, would throw interesting light on the nature of amblyopia.

Material and Methods

Three groups of eyes were examined: 20 eyes with strabismic amblyopia ranging from 6/15 to 6/60, 20 eyes with normal visual acuity (the sound eyes of the amblyopic patients served as this control group), and 10 eyes which showed amblyopia due to organic lesions, such as macular degeneration, optic nerve atrophy, or chorioretinitis.

The amblyopic patients were from 8 to 25 years of age; all had a manifest strabismus, or a history of such, and none had ophthalmoscopically visible fundus anomalies.

The examination was performed in a refraction range, the illumination of the chart being kept constant in all tests. Snellen charts were used at a distance of 6 meters. After the visual acuity had been determined in each eye, a different chart was used to avoid memorizing of the letters and the visual acuity was again measured, this time with a neutral density filter (Kodak Wratten gelatin filter No. 96, N. D. 3.00) before the eye to be examined. Two minutes of adaptation were allowed after the filter was slipped before the patient's eye. The results were scored in the following way.

Vision was expressed in reduced fractions, for instance, 6/6=1.0 or 6/12=0.5. The ratio between vision without and vision with filter was recorded by reducing the numerical readings to the ratio $1:x$, for instance,

$$\frac{\text{vision without filter}=0.5}{\text{vision with filter}=0.15}=1:0.3$$

Results

The normal eye invariably showed a ratio of reduction of visual acuity from 1:0.4 to 1:0.5, the mean being 1:0.48. The individual variations were minimal. This confirms Ammann's results, which showed among 100 normal patients a ratio from 1:0.3 to 1:0.5.

The behavior of the amblyopic eyes was strikingly different. In 6 cases, the visual acuity was only slightly reduced (from

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From the Department of Ophthalmology, State University of Iowa College of Medicine.

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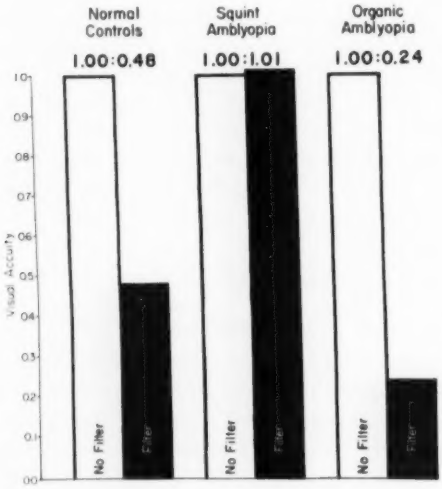
Visual Acuity Measurements for All Patients

Normal Controls			Squint Amblyopes			Organic Amblyopes			
Visual Acuity			Visual Acuity			Visual Acuity			
Without Filter	With Filter	Ratio	Without Filter	With Filter	Ratio	Without Filter	With Filter	Ratio	Disease
6/6	6/12	1:0.5	6/25	6/30	1:0.8	6/9	6/21	1:0.5	Glaucoma
6/6	6/12	1:0.5	6/15	6/20	1:0.7	6/9	6/30	1:0.3	Glaucoma
6/6	6/15	1:0.4	6/25	6/25	1:1	6/21	6/60	1:0.3	Chorioditis
6/5	6/12	1:0.4	6/60	6/60	1:1	6/12	6/60	1:0.2	Chorioditis
6/9	6/21	1:0.5	6/21	6/21	1:1	6/60	3/60	1:0.5	Retrobulbar neuritis
6/6	6/12	1:0.5	6/15	6/15	1:1	6/21	6/60	1:0.3	Retrobulbar neuritis
6/5	6/9	1:0.5	6/60	6/60+1	1:1.1	6/30	1/60	1:0.05	Congenital amblyopia
6/8	6/15	1:0.5	6/21	6/30	1:0.7	6/30	1/60	1:0.05	Congenital amblyopia
6/6	6/12	1:0.5	6/30−1	6/30	1:1.1	6/60	1/60	1:0.1	Macular degeneration
6/6	6/12	1:0.5	6/21	6/21−1	1:0.9	6/60	1/60	1:0.1	Macular degeneration
6/6	6/12	1:0.5	6/30	6/30	1:1				
6/8	6/15	1:0.5	6/60	6/60	1:1				
6/9	6/15	1:0.6	6/60	6/60	1:1				
6/6	6/15	1:0.4	6/15	6/15	1:1				
6/6	6/15	1:0.4	6/60	6/30	1:2.0				
6/9	6/21	1:0.5	6/21	6/21−1	1:0.9				
6/9	6/15	1:0.6	6/21	6/21	1:1				
6/6	6/12	1:0.5	6/15	6/15	1:1				
6/6	6/12	1:0.5	6/25	6/21	1:1.2				
6/6	6/21	1:0.3	6/25	6/30	1:0.8				

1:0.7 to 1:0.9); in 10 cases, the visual acuity remained essentially the same (1:1), and in 4 cases, it even improved under reduced illumination (from 1:1.1 to 1:2).



Average change for each group in terms of reduced fractions. Note that, whereas the filter reduces the visual acuity of the normal eye by about one-half and in eyes with organic amblyopia to about one-fifth, the vision of the eyes with strabismic amblyopia is on the average if anything slightly better with the filter than without it.

The third group of eyes, those with organic lesions, showed marked reduction of visual acuity (1:0.1 to 1:0.05), giving evidence of actual damage to the perceptor organs of the retina.

The raw data of the visual acuity measurements on all patients are given in the Table, and the average change for each group in terms of reduced fractions is represented in the Figure.

Comment

The startling results reported in this paper are of interest in several respects.

Decrease in illumination and, with it, decrease in contrast reduced the visual acuity of normal eyes with our technique by about one-half. No such decrease occurred when the same technique was employed with eyes having a strabismic amblyopia. Here the acuity remained the same, dropped only slightly, or actually showed an improvement. In contrast to this, eyes with reduced visual acuity due to pathologic changes showed an almost grotesque drop in visual acuity when the neutral filter was employed.

Comparison of the behavior of the eyes with strabismic amblyopia and of those with pathologic amblyopia indicates clearly that in the former we are not dealing with an affection of the rods and cones or of their neural connections, as such. Comparison of the behavior of the amblyopic eyes with that of the normal eyes points up the fact which has previously been established (Wald and Burian,[3] von Noorden and Burian [2]) that the amblyopic eye is not at its best under photopic conditions but that it shows a relative improvement of its functions under mesopic conditions. All the observations support the previously established finding of a selective functional suppression of form vision—a photopic function par excellence—in strabismic amblyopia (Wald and Burian [3]).

From a practical standpoint, application of the neutral-filter test can be of help in determining in doubtful cases whether or not an amblyopia is of pathologic or functional origin.

Summary

Visual acuity was measured with and without the use of a neutral filter in patients with normal eyes, with squint amblyopia, and with reduced visual acuity due to retinochoroidal or optic nerve lesions.

While the normal group showed a constant reduction of visual acuity, vision was only slightly reduced, remained the same, or even improved in the group of patients with squint amblyopia. The group with organic amblyopia showed a marked reduction of visual acuity.

A brief interpretation of these findings is given.

Department of Ophthalmology, University Hospitals.

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Tonography Under Constant Distention of the Sclera

E. PRIJOT, M.D., Liège, Belgium

Using Friedenwald's tonometric tables, Grant was able to measure the resistance * to outflow of aqueous humor in 1950. This new clinical method was conventionally referred to as tonography. It has acquired considerable practical importance in investigating the hydrodynamics of the aqueous humor.

One of the criticisms that may be leveled at tonography is the use of Friedenwald's coefficient of ocular rigidity.

According to the formula published by Grant, in 1950, the resistance to outflow can be calculated by means of the equation

$$R=\frac{\frac{Pt_1+Pt_2}{2}-Po}{\frac{1}{K}\log.\frac{Pt_1}{Pt_2}+Vc_2-Vc_1} \qquad (1)$$

where

R=the resistance to outflow of aqueous humor

Pt_1=the initial tonometric pressure, i. e., the pressure prevalent in the eye due to the weight of the tonometer at the beginning of tonography

Pt_2=the tonometric pressure at completion of tonography

K=the coefficient of ocular rigidity according to Friedenwald

Vc_1=the volume of the corneal indentation at the beginning of tonography

Vc_2=the volume of the corneal indentation at completion of tonography

Po=the ocular tension at the beginning of the test:

The factor $\frac{1}{K}\log.\frac{Pt_1}{Pt_2}$ =the reduction in the volume of the eyeball due to diminution of scleral distention when the ocular tension passes from value Pt_1 to value Pt_2:

$$V=\frac{1}{K}\log.\frac{Pt_1}{Pt_2} \qquad (2)$$

Submitted for publication Aug. 25, 1958.

From the Ophthalmological Clinic of the University of Liège (Prof. R. Weekers, M.D.).

* The resistance to the outflow of aqueous humor equals the reverse of the facility of outflow: $R=\frac{1}{C}$.

Calculation of the resistance to outflow of aqueous humour according to Grant's tonography thus is based on the validity of this coefficient of ocular rigidity (K).

However, recent publications (Toda, 1956; Perkins and Closter, 1957; Closter, Perkins and Pommier, 1957; Macri, Wanko, Grimes, and von Sallmann, 1957, and Prijot, 1958) have shown that this coefficient K is not constant. It varies with the ocular tension. The values of Equations 2 and 3 should consequently be accepted with caution.

The degree of the error introduced in tonography by the use of this coefficient of ocular rigidity can be evaluated by measuring ocular tension with the aid of an aplanation tonometer and by developing a method of tonography in which ocular rigidity plays no rôle. For this purpose it should be ensured that scleral distention be the same at the beginning and at completion of tonography. This can be effected in the following three ways: (*a*) by keeping tonometric pressure constant throughout tonography, while continually increasing the weight of the tonometer plunger (Moses, 1958; Van Beuningen and Fischer, 1958); (*b*) by adding a supplemental weight to the tonometer plunger during tonography in such a way as to cause tonometric pressure to exceed the initial value (Pt_1), terminating tonography when the tonometric pressure, with the added weight, equals the initial value Pt_1 (Goldmann, 1958); (*c*) by progressive overloading of the tonometer plunger at the end of classical tonography, i. e., after four minutes, until tonometric pressure returns to the initial value. I have recently described the principle of this last procedure as adopted by me (Prijot, 1958).

Whatever the procedure used, tonometric pressure is identical at the beginning and at the end of tonography. Isotonography is thus effected. At the end of the test, the scleral distention becomes similar again to that at the beginning, and the factor $\frac{1}{K}$ log. $\frac{Pt_1}{Pt_2}$ equals zero.

The resistance to outflow can then be calculated using the following equation, from which K is excluded:

$$R=\frac{Pt_{av}-(Po+1)}{Vc_2-Vc_1} \qquad (3)$$

Po=ocular tension measured in a sitting position with the aid of Goldmann's aplanation tonometer

Pt_{av}=the mean tonometric pressure throughout the duration of tonography

$Po+1$=ocular tension in a recumbent position (Goldmann, 1957)

This difference results from a modification in a similar sense in the episcleral venous pressure (Linnér, Rickenbach, and Werner, 1950; Stepanik, 1955; Leydhecker, 1956).

According to the technique suggested, the tonographic curve is thus divided into two periods, as follows: (*a*) the first period, of four minutes, during which tonometric pressure decreases, and (*b*) the second period, of variable duration, during which tonometric pressure rises again until it reaches its initial level.

The mean tonometric pressures during these two periods are identical. The mean tonometric pressure throughout tonography is equal to the arithmetical average of the initial tonometric pressure and the tonometric pressure at the end of the fourth minute.

In order to determine, in the second part of the tonogram, the moment at which the pressure reaches the initial value, we used the equation introduced by Friedenwald (1957):

$$Pt=\frac{W}{0.107+0.0138\,R} \qquad (4)$$

W=the weight of the plunger and its added weight and R, the tonometer scale reading

Vc_2=the volume of the corneal indentation at the end of tonography and cannot as a rule be determined by means of the Friedenwald tables

At the end of topography, the weight of the plunger and its load only seldom equals 5.5, 7.5, 10, or 15 gm., the only values for which Friedenwald set up a table. This author (1937, 1954), however, has shown that the volumes of corneal indentation may be calculated by means of the following equation:

$$\log.Vc=N\ (B-\log.Pt) \qquad (5)$$

B and N are coefficients whose value depends on the weight of the tonometer plunger.

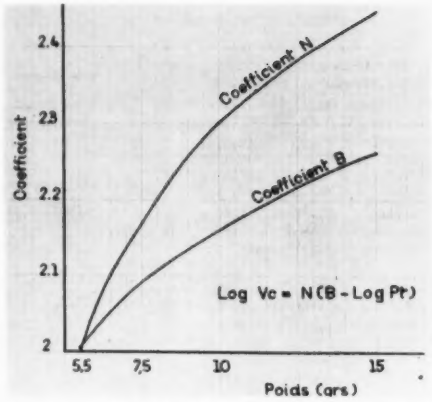

Fig. 1.—Graph indicating the value of coefficients B and N as a function of the tonometer plunger weight (Prijot, *Ophthalmologica*, 1958).

Friedenwald (1957) calculated these values for weights of 5.5, 7.5, 10, and 15 gm. With the aid of these values we have plotted a graph which makes it possible to calculate the values of coefficients for each intermediate value of plunger weight and load (Fig. 1).

If a certain approximation is accepted, it is also possible to calculate the final tonometric pressure and the volume of corneal identation (Vc_2) with the aid of Friedenwald's nomogram (1957).

Personal Technique and Results

I used the following instruments:

(*a*) A Goldmann aplanation tonometer (1954) (Haag-Streit-Bern).

(*b*) An electronic Mueller tonometer that met the requirements set up by the Committee on Standardization of Tonometers of the American Academy of Ophthalmology and Otolaryngology (V. Mueller & Co., Chicago).

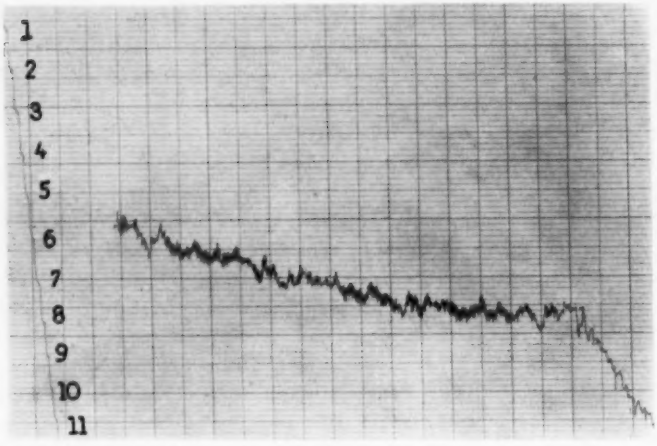

Fig. 2.—Tonogram in a normal subject. The interval between two vertical lines is 15 sec. The figures correspond to the tonometer scale reading. Their position was determined by means of the calibration curve seen immediately on their left. The tonogram is divided into two parts, namely, a first part, only slightly sloping, with increasing corneal indentation and diminishing tonometric pressure, and a second more markedly sloping part with the weight of the tonometer plunger being increased by 250 mg. every 3 sec. During this period the corneal indentation and the tonometric pressure increase. The latter reaches and then exceeds the level of the initial tonometric pressure.

(*c*) A series of weights † of 250 mg. to be placed on the top of the tonometer plunger.

(*d*) An electronic recorder (Speedomax, Type G recorder, model S 60000 series, designed by Leeds and Northrup Co., Philadelphia).

(*e*) A micrometer made of nonmagnetic material and designed to write on the recorder paper a curve of tonometer calibration (Hillecrest Engraving Co., Mayfield Heights, Ohio).

† Designed by L. Sanson, Laboratory of Experimental Surgery, University of Liège.

Determination of the resistance to outflow of aqueous humor is effected in the following stages:

(*a*) Local anesthesia by instillation of a 0.2% solution of benoxinate (Novésine, Dorsacaine).

(*b*) Determination of intraocular tension by means of a Goldmann aplanation tonometer.

(*c*) Tonography with the aid of an electronic tonometer.

(*d*) At the end of the fourth minute of tonography, progressive loading of the plunger with the aid of 250 mg. weights placed on the plunger every 3 seconds.

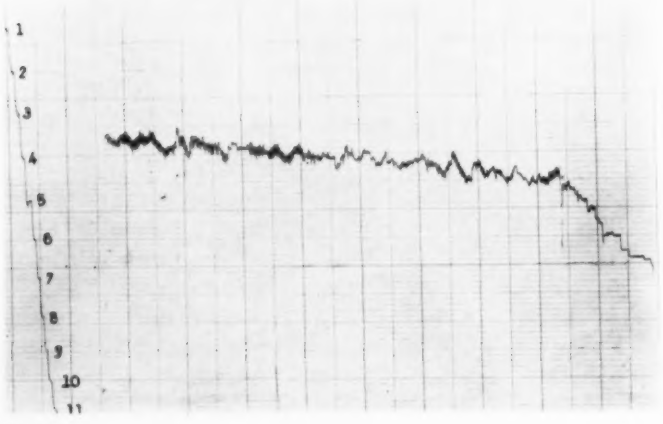

Fig. 3.—Tonogram in a glaucomatous patient (see legend for Fig. 2).

The end of the tonographic curve, i. e., the moment at which the tonometric pressure is equal to the initial tonometric pressure, is determined by means of Equation 4.

Pt_1, Pt_2, and Vc_1 are determined by means of the Friedenwald tables (1957). Vc_2 is calculated with the aid of Equation 5 and the graph in Figure 1.

Figures 2 and 3 show tonograms obtained by this method, by way of example.

Tables 1 and 2 present the results obtained in normal subjects and in patients with open-angle glaucoma, respectively. Values indicated for each case are intraocular pressure determined with the electronic tonometer and the Goldmann aplanation tonometer, resistance to outflow calculated by the Grant method, resistance to outflow according to the procedure suggested, and the ratio of the resistance values obtained by the two techniques.

TABLE 1.—*Results in Twenty Normal Eyes*

Ocular Pressure (Electron. Ton.), Mm. Hg	Ocular Pressure (Aplanation), Mm. Hg	Resistance to Outflow (Grant's Method), R_1	Resistance to Outflow (Personal Method), R_2	Ratio $\frac{R_2}{R_1}$
18.1	22.0	5.74	5.92	1.03
15.2	15.0	6.93	8.03	1.16
14.6	18.0	5.37	4.26	0.76
15.2	16.0	5.37	5.44	1.01
12.8	14.0	4.54	4.40	0.97
15.9	17.0	6.03	7.36	1.22
12.2	14.0	4.98	4.02	0.81
14.0	16.5	7.08	6.88	0.97
14.0	17.0	4.92	4.93	1.00
16.6	17.0	4.67	5.35	1.15
18.1	18.5	5.18	8.12	1.57
15.2	15.0	4.51	5.32	1.18
11.8	13.5	3.49	2.47	0.71
17.3	18.0	6.17	7.61	1.23
20.5	18.5	3.78	8.26	2.19
13.4	15.5	7.19	7.16	1.00
17.0	17.0	5.29	6.10	1.16
12.8	12.0	3.76	4.41	1.17
14.6	15.0	4.39	5.11	1.16
13.4	16.5	8.32	6.40	0.77
Mean 15.13	16.3	5.38	5.88	1.11
Standard deviation 2.29	2.50	1.53	1.53	0.59
Standard error of the mean 0.51	0.56	0.34	0.34	0.13

TABLE 2.—*Results in Eighteen Glaucomatous Eyes*

Ocular Pressure (Electron. Ton.), Mm. Hg	Ocular Pressure (Aplanation), Mm. Hg	Resistance to Outflow (Grant's Method), R_1	Resistance to Outflow (Personal Method), R_2	Ratio $\frac{R_2}{R_1}$
30.4	32.0	10.8	12.80	1.19
25.8	28.0	12.3	20.4	1.66
43.5	44.0	26.0	57.0	2.19
29.20	30.0	10.9	14.5	1.33
20.5	24.5	10.1	11.4	1.12
32.8	28.0	6.1	9.7	1.59
26.9	26.0	5.4	9.1	1.69
31.7	32.0	10.4	12.7	1.22
31.7	33.0	8.6	10.5	1.22
37.8	27.0	13.3	20.3	1.53
43.9	38.0	7.9	19.9	2.52
24.3	25.0	6.6	7.2	1.09
28.0	26.0	11.2	12.5	1.12
33.0	33.2	8.3	14.7	1.77
25.8	29.0	11.5	10.8	0.92
52.9	31.0	15.6	19.1	1.22
55.8	36.0	21.7	24.8	1.14
34.0	36.0	23.0	10.1	0.83
Mean		12.2	17.02	1.41
Standard deviation				0.40
Standard error of the mean				0.10

Comment

The criticisms currently developed with regard to tonography are numerous. In this paper an attempt has been made to evaluate the error introduced by using the equation:

$$V=\frac{1}{K}\log.\frac{Pt_1}{Pt_2}$$

For this purpose, results obtained in normal subjects and glaucomatous subjects by the Grant technique and by isotonography were compared.

In normal subjects the figures of resistance obtained by the two methods are of the same order of magnitude. The slight increase observed is not statistically significant.

In glaucomatous patients, on the other hand, the resistance values obtained by the method suggested are considerably in excess of those obtained by the Grant technique, the difference being statistically significant. The mean ratio of the two values is 1:40, with a standard error of the mean of ± 0.10.

By tonography in which ocular rigidity plays no role, higher resistance values are obtained in the hypertensive eyeball. Since the values obtained in normal eyeballs were

modified slightly or not at all, exclusion of Factor *K* from tonography can normally contribute toward a better differentiation between normal and pathological cases.

Conclusions

1. It is possible to effect tonography so as to exclude the factor of ocular rigidity.

2. The values obtained in normal subjects by this technique do not differ from those obtained by the Grant method.

3. Resistance values in glaucomatous subjects are considerably higher than those obtained by the method of Grant. The difference is statistically significant.

66, Boulevard de la Constitution.

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Corneal Crystals in Multiple Myeloma

SAMUEL B. ARONSON II, M.D., and RICHARD SHAW, M.D., Bethesda, Md.

Bilateral crystal-like deposits in the clear cornea or in the cornea and conjunctiva have received renewed attention in recent years, since it has become known that this clinical picture can denote such serious systemic diseases as cystinosis and multiple myeloma. Whereas adequate information is available on appearance, composition, and diagnostic value of such crystals in these ocular tissues of children with cystinosis, the nature and significance of similar deposits in patients with multiple myeloma awaits clarification. The uncertainty of the medical diagnosis in earlier case reports, the small number of pertinent observations, and the lack of histological identification of the crystals indicate that further studies on patients with multiple myeloma are warranted.

The patient described in this paper shares some of the features of the few previous cases and, thus, strengthens the diagnostic merit of the biomicroscopically visible signs. This patient also exhibits some changes which have not been recorded in other instances. Moreover, biopsy material could be obtained from the involved conjunctiva and subjected to extensive histological examination.

Report of a Case

The eye history of the 60-year-old white housewife dates back to the spring of 1952, when, during a routine examination in another hospital, a diagnosis of bilateral nonfamilial crystalline corneal dystrophy was made. Four years ago the patient experienced an attack of iritis of the right eye and, one year later, two episodes of conjunctivitis. They were considered allergic in nature. The conjunctivitis recurred in February, 1957. The patient was admitted to the National Cancer Institute in March of that year with the diagnosis of multiple myeloma based on results of bone-marrow studies and serum electrophoresis. Two months later she was seen in the Ophthalmology Branch of the National Institute of Neurological Diseases and Blindness, because of itching and burning sensations of the right eye. In addition to complaints possibly connected with conjunctival disease, the patient reported, on questioning, that she noticed minute scattered dots when gazing at a bright light source.

The examination did not disclose any signs related to the symptoms of conjunctivitis. There was no discharge. The eyes were white. The palpebral conjunctiva was not injected, and its surface was smooth. A visual acuity of 20/20 was obtained on both eyes with a correction of −0.5 O. D. and −0.75 O. S. The near vision was J1 O. U. with +1.5 sphere.

The cornea appeared clear and had normal luster and normal sensitivity to touch. Under the biomicroscope, masses of very fine irridescent crystalline deposits were seen interspersed through the corneal stroma and were densely packed in the anterior half of this tissue. The number of particles seemed to decrease gradually towards the posterior surface. In the center the cornea was involved to about 2/3 of its thickness and in the periphery, to about 1/3. The deposits reflected in all colors and were reminiscent of the tinsel effect of cholesterol crystals. Photographs (Figs. 1, 2) taken with the

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From the Ophthalmology Branch, National Institute of Neurological Diseases and Blindness (Dr. Aronson), and the General Medicine Branch, National Cancer Institute (Dr. Shaw), National Institutes of Health, Public Health Service, U. S. Department of Health, Education, and Welfare.

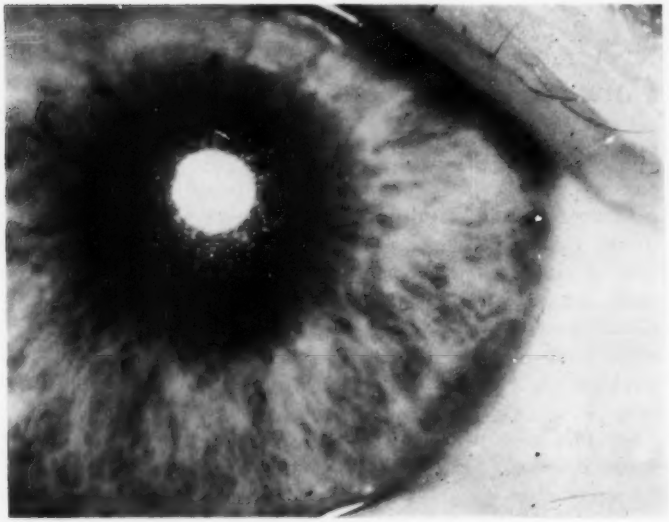

Fig. 1.—Crystals in the prepupillary part of the cornea.

Donaldson camera depicted the change only in the areas of specular reflection and did not fully illustrate the colorful brilliance of the biomicroscopic view. The corneal epithelium seemed free of deposits, but crystals less densely arranged were distributed through the superficial layers of the bulbar conjunctiva and were sparse in the tarsal conjunctiva. The remaining parts of the anterior segment showed no abnormalities. The lens and vitreous were clear and the fundi normal. The intraocular pressure was not increased.

The following significant laboratory findings were obtained: The serum proteins (7.9 gm. %) consisted of 2.2 gm. % albumin and 5.7 gm. % globulin. Electrophoretic analysis of the globulins gave the following results: α_1, 0.6; α_2, 1.4; β_1, 1.4, and γ, 2.3 gm. %. Tests for cryoglobulins and macroglobulins were negative. During the first admission of the patient the serum

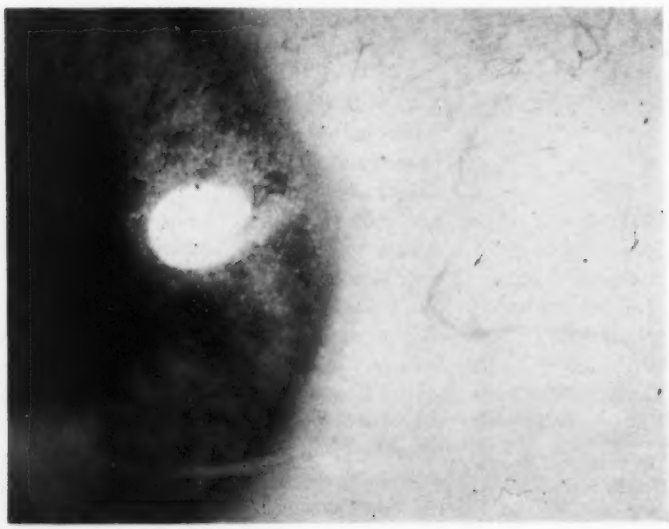

Fig. 2.—Crystals in the peripheral part of the cornea.

cholesterol did not exceed 166 mg. % on repeated analyses. Serum calcium (10 to 11 mg. %) and serum uric acid (4 to 5 mg. %) fell within the normal ranges. During the hospital stay the patient gradually developed a mild azotemia (BUN 50-60).

Bence Jones protein was negative in the patient's urine on several occasions. α-Amino-nitrogen determinations on the patient's 24-hour urine collections were normal on two occasions. Urinary protein electrophoresis showed a β-globulin comprising 50% of the material, whereas the serum contained a γ-myeloma protein. Hypercalcinuria has never been present.

In the report of x-ray examination a mild generalized osteoporosis was ascribed to an age change but was considered compatible with myeloma, although not diagnostic. Diverticulosis of the large bowel was diagnosed by barium enema.

Bone-marrow aspiration was carried out twice. Both sections and smears contained sheets of plasma cells, many of them immature, with centrally located nuclei and large irregular nucleoli, and were diagnostic of multiple myeloma. An unusual finding in 10% of the myeloma cells was the presence of many crystalloid structures in the cytoplasm, which were best visualized with phase microscopy (Fig. 3). In stained smears, colorless clefts in the basophilic cytoplasm indicated the position of the crystalloids. This suggested the possibility that they consisted of lipids which had been removed by alcohol fixation.*

In June, 1957, an oval piece of bulbar conjunctiva measuring 3 to 5 mm. in diameter was excised from an area adjacent to the limbus under local anesthesia; instillation of 0.5% tetracaine (Pontocaine) was supplemented with a subconjunctival injection of 2% procaine. The tissue was divided into three equal parts. One part was fixed in an alcohol-trichloroacetic-acid-formalin mixture; the second part was fixed in 10% cold formalin containing 2% calcium acetate, and the third part was frozen in liquid nitrogen. The first portion, imbedded in paraffin, did not show birefringent elements under polarized light. The Schultz method for cholesterol, the digitonin reaction for free sterols, and the von Kossa technique for cystine and calcium gave negative results. The formalin-fixed portion was subdivided to be studied (*a*) in frozen sections, (*b*) in sections after gelatin imbedding, and (*c*) as whole mount. A few Maltese crosses and fine needle-shaped luminous particles were visible in polarized light. Digitonin

* The phase microphotographs were taken by Dr. George Brecher, Chief, Hematology Service, Clinical Pathology Department of the Clinical Center.

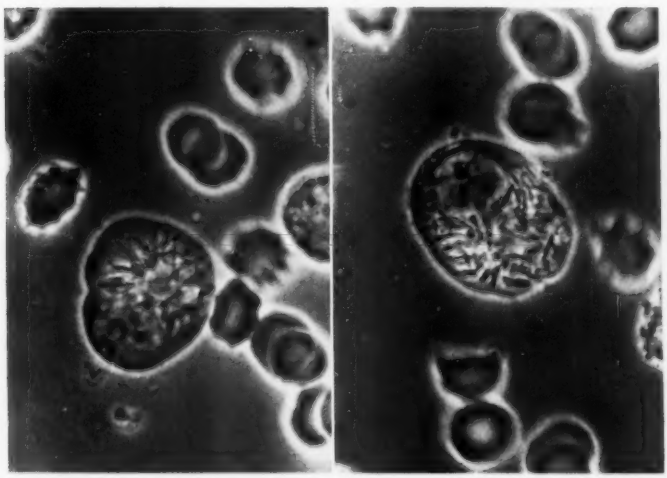

Fig. 3.—Needle-like crystals in plasma cells of the bone marrow (phase-contrast photographs).

cholesterid crystals were demonstrated with Windau's technique. As compared to sections, the whole mount was more suitable for demonstrating crystals. When the Schultz stain was applied to this preparation, a few blue-green patches were noticed which faded within a few hours.

The Weigerts-Pfister staining procedure and Masson's trichrome technique recommended by Sikl for demonstrating paraprotein crystals in kidney tissues did not stain or outline crystals in the conjunctiva.

The results were taken only as suggestive evidence for the presence of lipoids. Control material obtained from cat's adrenal glands exhibited the described staining properties far more convincingly than the conjunctival tissue. Some support of the impression of the lipid nature of the deposits was derived from the examination of tissue frozen in liquid nitrogen. After suspension of the material in formalin, several Maltese crosses could be identified in the whole mount (Fig. 4) and the Schultz stain was transiently positive in circumscribed spots.

Within one year, the distribution and characteristics of the irridescent crystals in cornea and conjunctiva did not noticeably change. During this period, the patient did not complain of eye discomfort and the visual acuity continued to be normal. An experimental course of O-diazoacetyl-L-serine (Azaserine, an antibiotic with antitumor effects) was given to the patient during her hospital stay, with no improvement in her clinical status or eye findings. The general course of the disease was stormy and necessitated repeated admission to the National Cancer Institute. Since a recurrent severe attack of jaundice due to intrahepatic obstruction had no relevance to the ocular signs, the listing of clinical and laboratory findings dealing with this phase

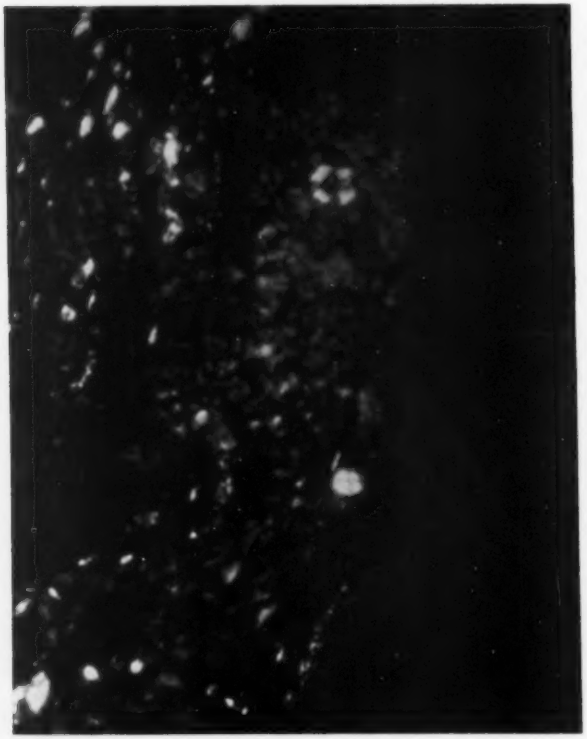

Fig. 4.—Maltese crosses in the conjunctiva after freezing in liquid nitrogen and suspension of the material in formalin.

of the disease is omitted.† Brief mention should be made of a short course of urethane and prednisone treatment prior to the patient's first admission. This was long after the crystals of the cornea and conjunctiva had been detected. Since her discharge she has been given urethan, with no improvement, and prednisone, with symptomatic improvement but no change in the results of laboratory or eye examinations. The patient is currently doing quite well with no treatment and has had no eye complaints for the last six months.

In an attempt to estimate the incidence of corneal change in multiple myeloma 13 patients with this diagnosis were examined biomicroscopically. None of these patients exhibited evidence of crystalline deposits in the cornea and the conjunctiva. In view of the small number of reported myeloma cases with corneal crystals it must be assumed that these deposits occur rarely in such patients.

Comment

Recently, E. Bürki [1] has given the first comprehensive account of the literature on corneal crystals possibly connected with multiple myeloma. Originally he considered his own case, which he described with Rohner [2] in 1955, as an example of crystalline degeneration of the cornea of unknown origin. At this time he stressed the similarity between the biomicroscopic picture and that associated with cystinosis of children. Further observations on this patient, however, enabled him to establish definitely the clinical diagnosis of multiple myeloma. The γ-globulin reached a level of 55.6%, and the albumin decreased to 32.49%. Bone-marrow aspiration revealed 21.5% pathologic plasma cells, partially arranged in clusters. Proteinuria indicated the involvement of the kidney, and in September, 1956, the patient died of uremia. The autopsy report of plasmocellular myeloma confirmed the clinical diagnosis. The cornea was subjected to histologic examination, but the chemical nature of the deposits could not be ascertained in sections of formalin- and alcohol-fixed material. Nevertheless, according to Bürki's opinion, there was little doubt that the crystalline deposits which he had observed for three to four years were paraproteins. Crystallization of abnormal globulins is considered to be the cause of variously shaped deposits in plasma cells and kidney epithelia, which have been occasionally demonstrated in patients with multiple myeloma. Cytoplasmic inclusions in these tissue elements have not been mentioned in the description of Bürki's patient.

Bürki lists and analyzes the case reports of Meesmann,[3] Palazon,[4] Blobner,[5] Palm,[6] and Markoff [7] and concludes from the data given that multiple myeloma was the most likely underlying systemic disease. The diagnosis was definite in Markoff's and Bürki's patients, was most probable in Meesmann's and Blobner's cases, and questionable in Palm's and Palazon's observations.

The case reported here is similar in several respects to that of Bürki and is briefly referred to in his paper (von Sallmann). However, the clinical appearance is almost identical with that described by Blobner, because in his case also crystals were dispersed in the cornea and conjunctiva and the deposits in the cornea exhibited a brilliant tinsel effect in the beam of the slit lamp. On the other hand, Meesmann observed masses of grayish-yellowish dots which did not reflect like crystals and were thought by him to be deposits of Bence Jones proteins. In Palm's and Bürki's patients the corneal periphery was free of crystals. Palm could resolve superficial fine opacities as cubical crystals. At variance with other observations, the surface of the epithelium was somewhat irregular. Palm proposed that he dealt with crystals of pathologic globulins. Markoff's observations on a patient with an established diagnosis of multiple myeloma differed considerably from those of other cases as far as the corneal pathology is concerned. The patient

† A report on the unusual jaundice has been submitted to another journal by Drs. Richard Shaw and Lennard Gold.

developed photophobia and inflammatory signs after days in which she was annoyed by foreign-body sensation. This occurred during a period of intensive systemic urethan treatment. The corneal change was characterized by diffuse cloudiness and dispersion of needle-like crystals. The central part of the left cornea was the seat of an epithelial defect. Symptoms and signs vanished when the urethan therapy was discontinued. Markoff believed the deposits were urethan crystals.

As in the patients of Meesmann, Blobner, and Bürki, the crystals in the cornea were seen in the presently described case a long time (five years) before the medical diagnosis was made. One bout of iritis had healed without residues. In Bürki's patient attacks of iritis complicated the eye disease.

Histological or histochemical examinations of corneal tissue have been attempted by Meesmann and Bürki, but the nature of the crystals could not be established by the investigators. Paraprotein crystals could not be demonstrated in biopsy material of the case presented here, although methods of staining and fixation were used which had been applied successfully by Sikl [8] to the kidney epithelium. Positive, although not striking, results of the examination in polarized light, with the digitonin reaction and the Schultz staining procedure, provide suggestive evidence that the crystals in this patient consisted of lipoids. This by no means excludes the possibility that in other patients crystals of paraproteins in the cornea are the basis of the conspicuous biomicroscopic change. Such a concept, however, requires further histologic proof.

Summary

A patient with multiple myeloma is described whose corneae were studded with irridescent crystals. They were seen five years before the systemic disease was diagnosed. The conjunctiva contained similar less densely arranged particles.

The examined biopsy material obtained from the conjunctiva strongly suggested that the deposits were cholesterol.

Needle-like crystals were contained in pathologic plasma cells in aspirated bone marrow.

Similarities and differences of the clinical changes between this patient and other scattered observations in the literature are discussed.

Dr. Ludwig von Sallmann did the histological studies of the eye tissue; Dr. George Brecher did the cytological examination of the bone marrow, and Dr. John Fahey did the serum and urine electrophoretic studies.

Ophthalmology Branch, National Institute of Neurological Diseases and Blindness, National Institutes of Health (14).

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Keratomycosis

A Report of Six Cases

DAVID BARSKY, M.D., Detroit

The complications of corneal infections are very easily forgotten now that antibiotics and corticosteroids are a common therapeutic regimen. It is well, therefore, to reemphasize that so-called antibiotic-resistant corneal infections may be due to fungi. Although the reported cases are relatively few, an increasing number have appeared in the recent literature. Reports by Ley and Sanders [1]; Roberts [2]; Schardt, Unsworth, and Hayes [3]; Ziobrowski,[4] and Veirs and Davis [5] have illustrated the difficulties in management of fungus infections.

Six enucleated eyes received in the Pathology Department of the Kresge Eye Institute since September, 1955, proved to have fungi demonstrable in corneal abscesses on histologic examination. In only one instance was clinical evidence of fungus infection obtained prior to enucleation. The six cases are herein reported as follows:

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From the Department of Pathology, Kresge Eye Institute.

Report of Cases

CASE 1.—This 59-year-old white man gave a history of getting sawdust and bark in his left eye in July, 1955. Subsequent to this he developed a corneal ulcer. The ulcer was treated at irregular intervals over a nine-week period, but the eye became intensely painful and the ulcer progressed. Clinically, a diagnosis of suppurative endophthalmitis was made. The eye was enucleated Sept. 20, 1955.

On pathological examination there was a ring abscess of the cornea; the stroma was infiltrated with fungi which had the appearance of Aspergillus. (The organisms were easily visible with the routine hematoxylin and eosin stain, Figs. 1 and 2). There was an associated hypopyon and anterior uveitis. The fungi extended through Descemet's membrane; however, the globe was not collapsed. Mycelia were present in the anterior chamber.

CASE 2.—This 65-year-old white man was first seen May 6, 1954, complaining of loss

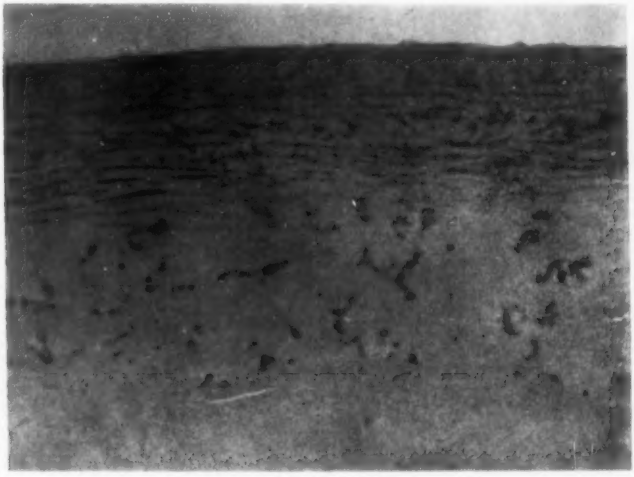

Fig. 1.—Photomicrograph of fungus keratitis; × 100.

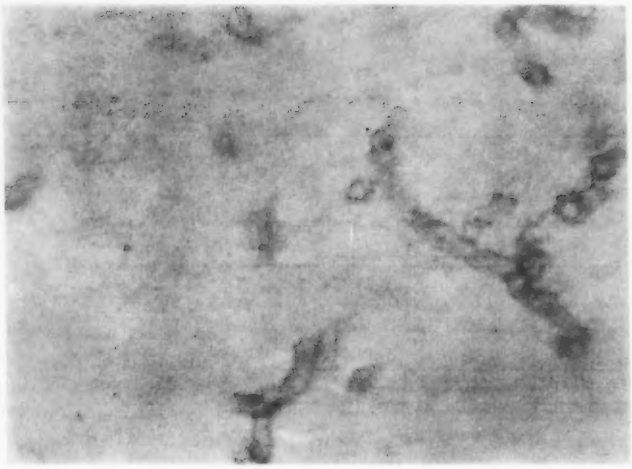

Fig. 2.—High-power view of fungi in cornea; × 420.

of vision over the previous six months. The intraocular tension was 40 mm. in the right eye, 46 mm. in the left eye. A diagnosis of chronic simple glaucoma was made. The patient was placed on 2% pilocarpine, and the tension was lowered to 19 mm. (Schiøtz) in the right eye and 23 mm. in the left eye. The patient did not return to his ophthalmologist until Jan. 7, 1957, at which time he was completely blind in his left eye and had a large corneal erosion centrally. The tension was 80+ mm. in the left eye and 26.5 mm. in the right eye. The patient refused further miotic therapy and medical care. He returned three weeks later, complaining of severe pain in the left eye. The globe had perforated, and it was therefore enucleated the same day.

On pathological examination, there was a through-and-through perforation of the cornea centrally, associated with purulent keratitis. A portion of the lens, some of the choroid, and part of the retina had prolapsed through this perforation. Mycelia were found palisading the anterior corneal surface, as well as scattered throughout the corneal stroma. The fungi were seen with moderate difficulty on routine hematoxylin-

Fig. 3. — Photomicrograph showing fungi in corneal abscess. Hematoxylin and eosin; × 100.

Fig. 4.—Same as Figure 3. Periodic acid Schiff; × 100.

and-eosin-stained sections; however, PAS staining demonstrated the organisms clearly (Figs. 3 and 4).

CASE 3.—This white woman was admitted to Detroit Memorial Hospital Oct. 18, 1957, with a diagnosis of corneal abscess of the left eye. Her general physical condition was within normal limits, aside from the ocular infection. Routine laboratory studies, including complete blood cell count and urinalysis, were normal. Treatment consisted of erythromycin (Ilotycin) P. O. and procaine penicillin G (Crysticillin) I. M.; topically, atropine and Neohydeltrasol were used. Cultures were taken from the conjunctival sac and from scrapings from the base of the ulcer before the antibiotics were begun. Direct smears were negative for bacteria, yeast, and mycelia. Blood-agar-plate and thioglycollate-broth cultures failed to reveal any growth. Lactophenol cotton-blue wet mount for fungi was negative. Cultures on Littman's and Sabouraud's media were negative up to six weeks.

On Oct. 21, Neodeltra Cortef was used topically without any apparent effect. The following day corticotropin (ACTH) was given along with tetracycline (Achromycin) ophthalmic suspension topically. Ten days later the corticotropin was discontinued and sulfacetamide sodium (Sodium Sulamyd) drops and neomycin ointment were used topically. Despite intensive therapy, the cornea perforated and the globe was enucleated.

Pathologic examination revealed the following findings: Severe purulent keratitis with corneal perforation adjacent to the anterior pole, through which there was a partial prolapse of ocular contents, including the iris, lens, and retina. Branching hyphae-like bodies were seen in the cornea and in the purulent mass posterior to this, suggestive of fungus infection. Hypopyon with purulent iridocyclitis. Endophthalmitis.

Fig. 5.—Photomicrograph showing corneal perforation secondary to fungus keratitis; × 3.

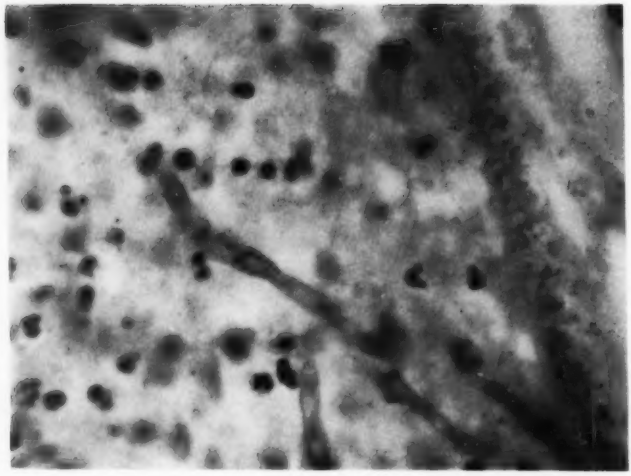

Fig. 6.—Photomicrograph showing fungi in anterior chamber; × 420.

Vitreous hemorrhage. Choroidal detachment with massive choroidal hemorrhage. Retinal detachment with subretinal hemorrhage (Figs. 5 and 6).

CASE 4.—This diabetic white man gave a history of being struck in the left eye by a tree limb. Four days later a corneal ulcer developed, and within two days severe hypopyon appeared. A clinical diagnosis of endophthalmitis was made. The eye became totally blind, painful, and inflamed. The globe was enucleated Dec. 14, 1957, just three and one-half weeks after the initial injury.

On pathological examination there was a central purulent ulcer with necrosis of the stroma leaving only Descemet's membrane intact, although bulging forward. The corneal stroma was diffusely infiltrated with filamentous hyphae of fungus origin. Hypopyon with acute iridocyclitis. Vitreous abscess. Endophthalmitis.

CASE 5.—The globe of a 41-year-old white woman was received in the laboratory without history on Feb. 10, 1958. Pathological examination revealed purulent corneal ulcer with necrosis of the superficial stroma. Diffusely scattered between the

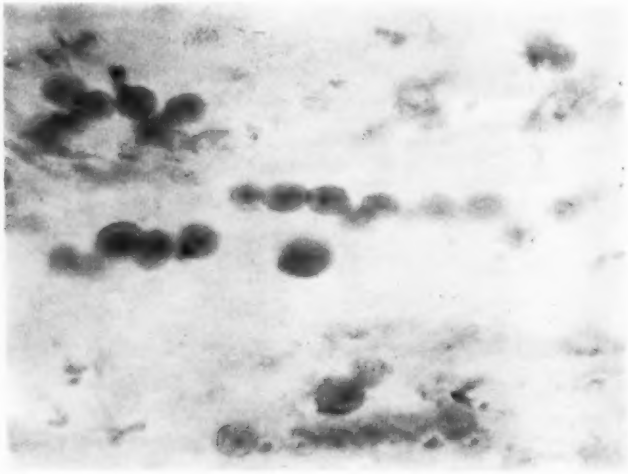

Fig. 7.—Yeast-like bodies in corneal stroma; × 420.

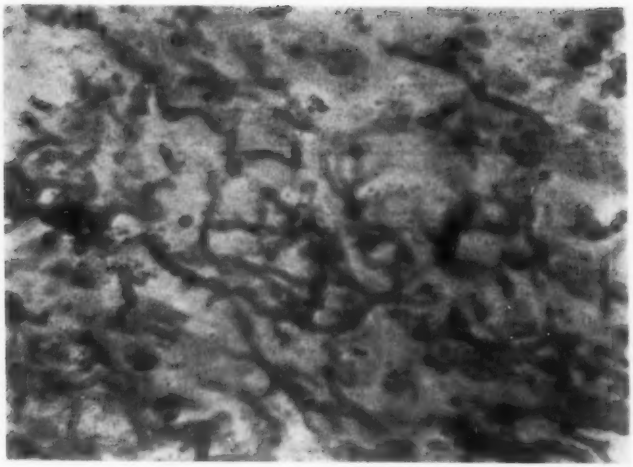

Fig. 8.—Fungus keratitis. Fusarium oxysporum was isolated and cultured; × 100.

lamellae were oval basophilic-staining bodies approximately three times the size of a polymorphonuclear cell. The yeast-like bodies had a deep-staining basophilic nucleus and were arranged in chains, in pairs, and singly. Descemet's membrane was involved by the infiltration (Fig. 7). There was a purulent iridocyclitis with hypopyon.

CASE 6.—This 77-year-old white woman had a history of a chronic corneal ulcer with hypopyon which went on to perforation. Prior to enucleation, a fungus was recovered from the corneal ulcer and identified as a member of the Fusarium group. (Dr. F. L. James, Pathologist at the Port Huron Hospital, submitted this specimen to us, with the notation that this apparently was the third such case reported in the literature.[6,7]) The specimen was received March 19, 1958.

On pathologic examination there was a massive purulent ulcer involving the anterior pole, with marked necrosis of the corneal lamellae. Multiple hyphae were scattered between the lamellae. The organisms appeared to be of fungus origin, comparable with Fusarium oxysporum (Fig. 8).

Comment

Fungus keratitis is usually secondary to a foreign-body injury. The spores may be carried on a foreign body or may be present in the air, particularly in rural or farming communities. Thorns, chips of wood, or strands of hay or straw initiate the break in the corneal epithelium and afford a bed for the spores to germinate within. It is very likely that steroids reduce the natural inflammatory response of the cornea to fungi, and, thus, the use of antibiotic-corticosteroid combinations for corneal ulcers merely enhances the possibility of fungus infection. Ley [8] has shown experimentally that the incidence of fungus keratitis in cortisone-treated eyes was 80%, in contrast to 20% incidence in the control group. Mitsui and Hanabusa [9] have shown that the use of cortisone topically raises the incidence of fungi in conjunctiva to 67% from the control level of 18%. It would seem, therefore, logical to conclude that corticosteroids are contraindicated whenever fungus infection is suspected.[10]

Cultures of conjunctival discharge should be grown on special media, such as Sabouraud's, to identify the fungi. Practically, corneal scrapings are more desirable because the cultures of the discharge alone are often negative for the fungi. (Even when the fungi are isolated, their pathogenicity should be verified.)

It is very conceivable that fungus infection may be overlooked on pathologic examination in sections stained with the normal hematoxylin and eosin methods. Unless

corneal abscesses are specifically stained with differential stains, such as periodic acid-Schiff or Gomori's methenamine and silver, the identification of fungi may be difficult. The growing awareness on the part of the pathologists that fungus infections are becoming more prevalent is made manifest by the increasing demands for differential stains whenever ocular infections are encountered.

It might be added that clinically all cases herein examined revealed a dense purulent keratitis with hypopyon. Microscopic examination disclosed the fungi boring through Descemet's membrane without causing collapse of the anterior chamber; it is, therefore, presumed that the presence of the fungus or its toxin in the anterior chamber is the cause of the hypopyon.

At present, unfortunately, even when the diagnosis of fungus infection is made, treatment is unsatisfactory. Local curettage, cautery, and systemic and topical iodides and sulfonamides have been used with limited success. The possibility that the mycostatic agents, such as nystatin,[11,12] amphotericin B,[13,14] or trichomycin,[9] might be effective topically has been proposed.

Summary

Six cases of fungus infection of the cornea, which led to enucleation, are reported. The fungus was demonstrated on microscopic examination, although only in one case was the organism identified clinically. The need for awareness of mycotic infections of the cornea is stressed.

The cases were contributed by Drs. C. D. Townes, Louisville; H. E. Holden, Lakeland, Fla.; J. W. Webb, Jonesboro, Ark.; R. A. Keffler, Lubbock, Texas, and N. Douvas and F. L. James, Port Huron, Mich.

Dr. W. S. Davies, Pathologist, Kresge Eye Institute, gave assistance in this report.

Photomicrography by Sesta T. Matheison.

Kresge Eye Institute, 690 Mullett St. (26).

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Arcus Senilis

Its Pathology and Histochemistry

DAVID G. COGAN, M.D., and TOICHIRO KUWABARA, M.D., Boston

Arcus senilis is a name applied to an opacity of the peripheral cornea occurring in persons of middle age or older. Generally separated from the limbus by a clear interval, it has a mat-white or yellow-white color and only when very dense does it contain scintillating crystals. The entire thickness of the corneal stroma may be involved but less extensively in the midstroma, and so the distribution of the opacity is usually that of an hour-glass. The most extensive involvement is that adjacent to the posterior surface (Descemet's membrane).

While present to some extent in all persons past middle age, an arcus is also present occasionally in young persons (arcus juvenalis) and is particularly common in persons with familial hypercholesteremia and xanthomatosis.[1-6] Its association with hypercholesteremia from other causes (myxedema, diabetes, lipid nephrosis) has been suggested but is equivocal.[7-9] The opacity of the cornea occurring in the hypercholesteremic rabbit is sufficiently different from the arcus of man that, contrary to common practice,[5,10] it should not be accepted unreservedly as the counterpart of arcus senilis.[11]

Arcus senilis has intriguing systemic implications. It is reasonably certain that if we could properly interpret the factors involved in the formation of arcus senilis we would have useful information for the understanding of fat deposition elsewhere in the body, such as the so-called "fatty streaking" of blood vessels.

The studies to be reported in this paper were undertaken primarily to provide a pathologic description of arcus senilis examined by modern histologic methods and to determine by histochemical means the nature of the fat that makes up arcus senilis.

In view of the frequency with which arcus occurs in senile eyes, it is surprising that only a few comprehensive studies[12,13] have been directed to its pathology. In fact, little has been added since Takayasu[14] showed by means of Sudan dyes, and Parsons[15] later confirmed by means of Sudan staining and solubility studies, that fat deposition was the prime abnormality. Prior to this it had been claimed by no less authority than Leber[16] that arcus senilis was a form of calcareous degeneration and Fuchs[17] that it consisted of hyaline concretions. The idea that it is a degenerative change has persisted to the present despite protestations to the contrary,[13] and one generally finds arcus senilis still categorized in texts under the heading of degeneration. One of the secondary purposes of this paper therefore is to show that arcus senilis does not show the necrosis or atrophy which are prerequisites of degeneration.

Notes on Some Clinical Manifestations of Arcus Senilis

Unless it is marked, the arcus is separated from the limbus by a relatively clear area of cornea. This clear interval appears to be a function of the vascularity of the limbus rather than of any intrinsic factor in the cornea itself, for when, for whatever reason, a vascular arcade extends into the cornea, the arcus shows a corresponding deflection

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Howe Laboratory of Ophthalmology, Harvard Medical School, and Massachusetts Eye and Ear Infirmary.

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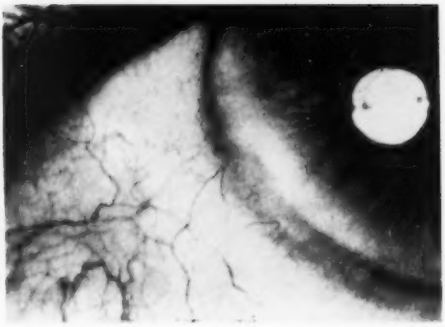

Fig. 1.—Arcus senilis showing an indentation corresponding to the extension of blood vessels across the limbus.

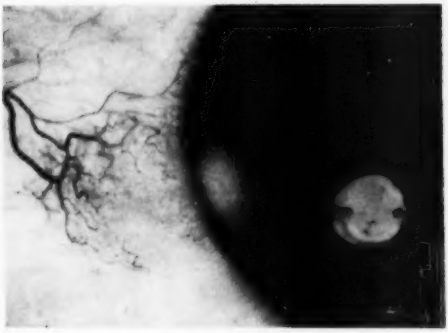

Fig. 2.—Localized arcus in area corresponding to vascular tumor (nevus) of the paralimbal region.

with a clear zone between it and the blood vessels (Fig. 1). While thus avoiding the blood vessels, the arcus seems to depend nevertheless on the blood vessels, for when there is an area of increased vascularity at the limbus, as from a tumor, the arcus will form preferentially in that corresponding portion of the cornea[5] (Fig. 2). One thus gains the clinical impression that, while sparing the immediate vicinity of the blood vessels, the arcus is nevertheless dependent on the blood vessels for its formation.

A few other clinical features of arcus are noteworthy. It contains scintillating crystals only when extremely marked. Rarely does it show the "crystalloid" edges which are characteristic of fat deposit in other types of lipid keratopathy, and the opacity is not appreciably fluorescent with radiations in the long ultraviolet range.

Except for the case of furrow keratopathy,[18,19] where the association with arcus is of questionable significance, there is no evidence of inflammation or ulceration resulting from an arcus.

Pathology

Observations of pathologic changes were made on approximately 25 eyes obtained through the facilities of the Boston Eye Bank. These were cut in the frozen state sometimes before fixation and sometimes after fixation with formaldehyde solution. All were stained with Sudan IV (counter stained with hematoxylin), and most were stained with hematoxylin and eosin. Some were stained by other means to be noted separately.

The chief pathologic changes were evident with the Sudan stains, and these will be described in some detail. The sections stained with hematoxylin and eosin and with the Van Gieson stain showed no abnormality. Specifically, there was no detectable increase in cellularity, no fragmentation of the laminae, no phagocytosis, and no unusual vascularity. Sections stained by means of cresyl violet and toluidine blue showed the normal distribution of metachromatic substance, with no alteration in the region of the arcus. The sections stained by the periodic acid-Schiff technique also showed no abnormality (but it should be noted that this also involved use of an organic solvent and so the fat was dissolved out in the process of staining). Finally, an indication that the cells in the region of the arcus were capable of enzymatic activity was obtained by incubating excised pieces of cornea in serum and oleate according to a technique previously described.[20] The pieces from the region of the arcus showed the same capacity for lipogenesis as those from regions not showing the arcus or as those from control corneas showing no arcus.

In contrast to the negative findings with the stains directed to protein and carbohy-

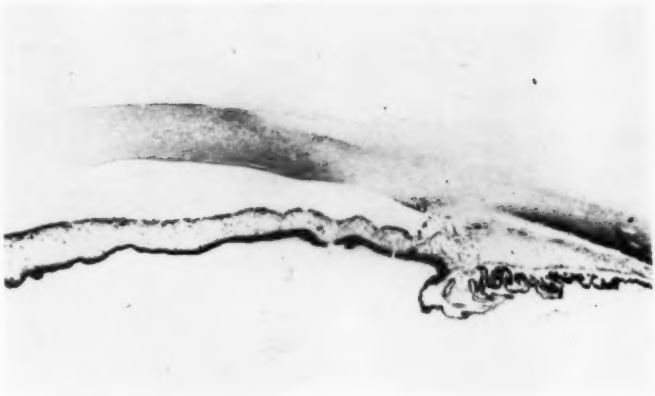

Fig. 3. — Characteristic distribution of fat in eye with arcus senilis. The section, stained with Sudan, shows staining of Bowman's and Descemet's membranes and of corneal stroma and sclera with sparing of the limbus (vascular zone).

drate components, those directed to study of fats showed uniform abnormalities that differed only in degree. The intensity of sudanophilia varied in the following decreasing order: Descemet's membrane, sclera, Bowman's membrane, and corneal stroma (Fig. 3). These will be described separately.

The minimal manifestation of an arcus senilis is a sudanophilia of Descemet's membrane. This has a characteristic hyaline quality unlike the granular sudanophilia of the corneal stroma. It involves the peripheral portions of Descemet's membrane but tends to spare, curiously, the most peripheral 0.25 mm. of the membrane. While of questionable significance, it tends to spare that portion of Descemet's membrane which is normally surfaced by an attenuated endothelium.

The sudanophilia of Decemet's membrane affects preferentially the anterior half of the membrane, and in the early stages it presents two distinct laminae: one lamina of sudanophilia adjacent to the stroma and one, separated from the first by a relatively unstained zone, situated in the approximate middle of Descemet's membrane (Fig. 4). This feature, which does not appear to have been described previously, is a relatively constant finding in early cases and may be present in the axial regions of more ad-

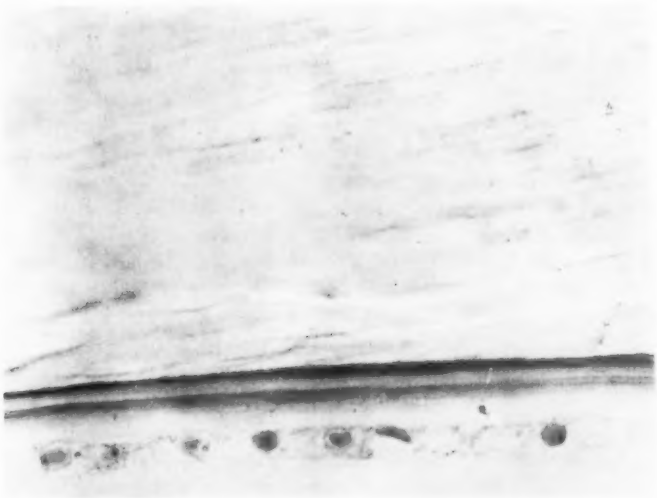

Fig. 4.—Double lamina of sudanophilia in Descemet's membrane.

Fig. 5. — Relative absence of sudanophilia about emissary vessel in the sclera.

vanced cases. No explanation for this double lamination occurs to us, but a somewhat analogous lamination of the posterior portion of Descemet's membrane has been noted for the deposition of copper in Descemet's membrane with hepatolenticular degeneration.[21]

Sudanophilia of the sclera is also a constant finding with arcus, even of mild degree. This sudanophilia involves the full thickness of sclera, but it is most dense in the region overlying the ciliary body. The limbal area is relatively spared. There is also characteristic sparing of the region immediately about the emissaria that perforate the sclera (Fig. 5).

The sudanophilia of the sclera consists of red dots, generally so small as to be at the limit of resolution, superimposed on and between the laminae. The scleral cells appear normal and show no intracellular lipid except when the arcus is very marked. Sizeable globules are present in the sclera also only when the arcus is extensive.

Bowman's membrane develops a sudanophilia when the arcus is of moderate degree. It consists of a hyaline type of sudanophilia like that of Descemet's membrane, but, unlike this latter membrane, the sudanophilia of Bowman's membrane extends to the extreme periphery. Thus the anterior portion of an arcus has a sharp peripheral terminus in contrast to the posterior portion, which is ill-defined. This abrupt end of the arcus anteriorly is evident both clinically and pathologically.

The sudanophilia of the corneal stroma is like that of the sclera but never so intense. It increases toward the periphery but spares the limbal portion of the cornea. It has a granular appearance in sections and shows no staining of the corneal cells.

In summary, an arcus senilis shows no degenerative or morphologic abnormality other than a deposition of sudanophilic material in the cornea, particularly in the peripheral portions of the hyaline membranes and superimposed on the stromal laminae. Eyes showing an arcus of any degree also show a considerable sudanophilia of the anterior sclera. In other words, an arcus of the cornea is part of a paralimbal lipid infiltration of the corneoscleral coat, with characteristic sparing of the limbus itself.

Histochemistry

Sections from the foregoing cases were subjected to various staining procedures, solubility studies, and other means of examination for the purpose of identifying the fat present. These are presented so far as possible in table form with values repre-

TABLE 1.—*Histochemical Properties of the Lipid in Arcus Senilis*

	Bowman's Membrane	Stroma	Descemet's Membrane	Sclera
Sudan	+	+	+++	+++
Nile blue (formazan)	±	±	++	+++
Osmic acid	0	0	0	0
Baker's acid hematein	0	±	++	+
Liebermann-Burchardt	++	+	+++	++++
Metachromasia				
Cresyl violet	0	0	0	±
Toluidine blue	0	0	0	0
Birefringence	0	0	0	0
Fluorescence	++		++++	

senting in each case a number of separate observations.

1. *Staining and Physical Procedures.*—Sudan: While the amount of sudanophilia varied according to the severity of the arcus, that presented in Table 1 represents an arcus of moderate degree.

It is generally believed that sudanophilia characterizes a nonspecific lipid in which Sudan will dissolve. Accordingly, this stain might be interpreted simply as indicating a neutral glyceride or cholesterol ester of sufficiently low melting point to dissolve the dye. Yet the hyaline quality of the sudanophilia of Descemet's and Bowman's membranes makes one question the validity of the thesis that the dye is merely dissolved in a lipid reservoir. Obviously more data are needed on the basis of Sudan staining before any far-reaching conclusions can be drawn from the Sudan-stained material.

Nile Blue: The formazan form of Nile blue is a rose color and, like Sudan, is believed to color those lipid substances in which it dissolves. With an arcus it has the same distribution as Sudan and therefore corroborates the suggestion that the lipid of an arcus is a neutral glyceride or cholesterol ester, but it adds nothing new. The fact that it stained Descemet's membrane and the sclera but not always Bowman's membrane or the corneal stroma probably reflects its lack of sensitivity rather than any qualitative difference.

Osmic Acid Reduction: This is an index of unsaturated fats when controlled by duplicates run on defatted sections. Under most biological conditions it is an index of an oleate component and is positive in most of the fat reservoirs of the body. The fat of an arcus shows no blackening with osmic acid, indicating a surprising lack of unsaturated fats in arcus senilis or, what is more likely, an insufficient amount present to be evident with this relatively insensitive method. This failure to blacken with osmic acid was noted early [22] and accounts largely for the original denial that arcus senilis was a fatty change.

Baker's Acid Hematein Method: This is a procedure which is believed to be specific for phospholipid when controlled by pyridine extraction. In the case of arcus senilis, it appears to be positive in those areas that have the greatest concentration of fat. Elsewhere phospholipid is presumably present but in too low a concentration for the sensitivity of the method. Even in areas of maximum lipid deposition with severe arcus the stain was only moderately positive (++), whereas by comparison myelinated nerve fibers and red blood cells in the same sections were strongly positive (++++). Thus, phospholipid is present in arcus in only moderate concentration.

Liebermann-Burchardt Test: This test showed a positive reaction for the entire area of the arcus. It had the same distribution and relative intensities as did the sudanophilia. This test is believed to demonstrate unsaturated sterols, and in most tissues this is presumed to be cholesterol.

One cornea having a conspicuous arcus senilis was fixed by 15 hours' immersion in 50% ethyl alcohol (ethanol) saturated with digitonin. This was then sectioned in the frozen state, again exposed to the ethanol and digitonin, and examined with crossed polaroids. Some birefringent crystals were then seen in the deeper layers of the sclera but none in the cornea. This is interpreted as indicating an absence of unesterified cholesterol in the cornea with arcus senilis.

Birefringence: In fresh unstained sections birefringence was uniformly absent, indicating that the lipid, whether it be a cholesterol derivative or a glyceride, is not crystalline at room temperature.

Fluorescence: Descemet's membrane and, to less extent, Bowman's membrane were definitely fluorescent in the region of the arcus. (Zeiss High Pressure Mercury-Vapor Lamp and filters, B. G. 12 [I] and U. G. 2 [III]) Control observations on a Descemet's membrane without arcus showed no fluorescence.

2. Solubility Studies.—The general procedure for testing the solubility of the lipid was to cut frozen sections 20μ thick, dry them on a slide, and then immerse them in various solvents. After predetermined times, the sections were removed from the solvent, washed in water, and stained with Sudan. If the lipid had disappeared with immersion after a few seconds, it was said to be very soluble (v. s.); if after a few minutes, it was said to be soluble (s.); if only slight diminution in the sudanophilia occurred after 20-30 minutes, it was said to be slightly soluble (sl. s.), and if no change occurred after one hour's immersion, it was said to be insoluble (i. s.).

Table 2 indicates that the lipid is soluble to a considerable extent in all organic solvents except acetone. It is most soluble in chloroform and methanol. Acetone results in only partial extraction of the lipid. On the other hand, the lipid is insoluble in aqueous solutions over a wide range of hydrogen ion concentration.

TABLE 2.—*Solubility of the Lipid in Arcus Senilis* *

	Bowman's & Descemet's Membranes	Corneal Stroma	Sclera
Ethyl alcohol			
100%	s.	sl. s.	s.
80%	i. s.	i. s.	
Methanol	s.		
Ether	s.		
Acetone	sl. s.	sl. s.	s.
Chloroform-methanol	s.	s.	v. s.
HCl, pH 2	i. s.	i. s.	i. s.
NaOH, pH 11	i. s.	i. s.	i. s.

* v. s. indicates very soluble; s., soluble; sl. s., slightly soluble; i. s., insoluble.

These staining and solubility studies indicate that the lipid of arcus and the associated lipid in the sclera consist of noncrystalline phospholipid and cholesterol in some form or other. A glyceride is also probably present, but this could not be determined for want of a suitable histochemical test.

Comment

The clinical and pathologic features of arcus senilis suggest that it is dependent for its localization on the blood vessels, probably as the source of the lipid, and yet it does not form in the immediate vicinity of the vessels. The reason for this paradox is not apparent, and nothing in the present observations clarified it. However, one might postulate that that component which stabilizes the lipid in the blood is lost by diffusion or by binding in tissue so that it is no longer able to maintain the lipid in solution except in the immediate vicinity of the vessels. This has been previously suggested to account for the occasional deposition of fat in the cornea with hyperlipemia.[23] An analogous process has been postulated for the formation of atheroma, in which the phospholipids have been thought to act as cholesterol stabilizers.[24]

The nature of the fat and of its binding to the cornea can be expressed in general terms only. It appears to be a mixture of cholesterol, phospholipid, and possibly other noncrystalline components. The fact that it may be present in relatively massive amounts, together with the absence of underlying degenerative changes, indicates it is of exogenous origin rather than derived from liberation of preformed fat. The obvious probability is that it is derived from the blood and becomes secondarily bound to the tissue. We have, however, been unable to demonstrate any particular affinity of the cornea, like that found in arcus senilis, to a mixture of lipids comparable to that of the arcus. Thus, although egg yolk contains phospholipid, cholesterol, cholesterol esters,

and neutral fat, it will bind only to the corneal stroma and not to Descemet's or Bowman's membrane. This was tested by injecting egg yolk into excised corneas, both human and rabbit, and by incubating the corneas in a mixture of egg yolk and serum. In no case did we succeed in producing the sudanophilia of Bowman's and Descemet's membranes, which is characteristic of arcus senilis.

Summary

Arcus senilis consists of a peripheral corneal opacity that depends on the presence of proximal blood vessels but yet spares the immediate environs of the blood vessels. Pathologically it is characterized by a hyaline sudanophilia of Descemet's and Bowman's membranes and a granular sudanophilia of the corneal stroma. It is invariably associated with a similar sudanophilia of the anterior sclera. The sudanophilia of Descemet's membrane is noteworthy in that it tends to spare the most peripheral portion of this membrane and, in its early stages, it involves preferentially the anterior half of this membrane in the form of double laminae. The sparing of the limbus is apparently due to the vascularity of this region.

The fat of arcus senilis gives the histochemical and solubility features of cholesterol, phospholipid, and neutral fat. It appears to be derived from the blood and is not dependent on any degenerative change in the cornea. We were unable to induce any similar binding in vitro by a comparable mixture of lipids from egg yolk.

243 Charles St. (14).

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Lens System Designed for Water-to-Air Vision in the Submerged Human Eye

T. D. DUANE, M.D., Ph.D.; R. J. EMRICH, Ph.D., Bethlehem, Pa., and CAPT. H. G. SHEPLER (MC), U. S. N.

The requirements for air-to-air, air-to-water, and water-to-water vision, except for minor complications, are relatively easily attained by the normal human eye. Because of the internal reflection and because the human eye is primarily adapted to air vision, therefore, the novel requirements demanded in water-to-air vision present an interesting challenge. One method of accomplishing this task and the means employed is the subject of this report.

The Problem

Water-to-air vision can be attained in a number of ways, but the following limitations were placed upon the designs of any lens system which we were to develop:

(*a*). It was necessary for water (index of refraction, $n=1.33$) to be in direct contact with the globe: This eliminated from consideration contact lenses, ordinary underwater goggles, helmets, periscopes, and the like.

(*b*). The eye was assumed to have an over-all index of refraction of 1.33.

(*c*). The apex of the cornea was to be approximately 7.8 cm. from a vertical parallel-sided 1.2 cm. plastic window, which separated the water from air.

(*d*). The vertex distance (apex of cornea to posterior lens surface of any desired auxiliary lens system) was assumed to be 1.33 cm.

(*e*). The subjects were to be normal young men with minimal inherent refractive errors.

(*f*). The maximum vision possible (i. e., distance acuity, near acuity, width of visual field, range of accommodation) was the desired goal. It should be noted that the maximum vision from water-to-air in the unaided submerged eye is equivalent to approximately halfway between the clinical states of light perception and gross hand movements.

The Solution

In general, for light rays to be brought to a focus by a lens system two requirements are set: (1) There must be a curved surface between object and image, and (2) there must be a difference in the index of refraction between the media. It is apparent from Figure 1 that some type of convex lens between the object and the eye is necessary to form an image on the retina. The ordinary refracting power of the eye (about 58 D.) is chiefly through the action of the cornea. The latter functions so effectively because of its curvature and more importantly because of the index of refraction

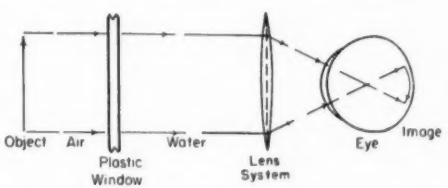

Fig. 1.—Schematic diagram of anticipated path of light rays from object in air to eye submerged.

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Consultant, U. S. Naval Air Development Center (Dr. Duane); Physics Department, Lehigh University (Dr. Emrich), and Director, Aviation Medical Acceleration Laboratory, U. S. Naval Air Development Center (Capt. Shepler).

difference between the air ($n=1.00$) and the ocular tissues ($n=1.33$). Taken together these factors account for 42 D. of the total refractive power of the eye, almost all of which is totally annulled in the limitations set by this experiment where the eye is submerged in water ($n=1.33$).

Several methods of overcoming this obstacle were considered. One approach was to insert a biconcave air-filled lens system between the eye and the face plate. The advantages were that it would be light in weight (it could conceivably be made of plastic) and that the benefit of air ($n=1.00$) in the lens to water ($n=1.33$) surrounding it would operate to reduce the dioptric power required. The disadvantages were that this was a very unusual form of lens construction, especially with reference to its watertight properties, and therefore construction would involve increased costs, and delays. Also, the rather high curvatures involved would result in a lens extremely thin in the center and therefore friable and delicate and not well adapted to the stresses anticipated. The latter difficulties could be somewhat obviated if the lens were constructed of plastic.

Having decided upon a biconvex system, we resolved to take advantage of glass with the highest index available. Inquiries made at several optical research laboratories revealed that glass of $n=1.9$ was available. Unfortunately, this glass was radioactive, unstable when exposed to air and other gases, very difficult and unreliable to grind accurately in the powers demanded, and inordinately expensive.

Flint glass, $n=1.7$, was readily available and was therefore chosen. The preliminary calculations indicated the following:

The lens system should be placed in water 37.4 mm. (length of eyeball, 24.4 mm., plus vertex distance, 13 mm.) in front of the retina. In other words $\frac{1,000}{37.4}=27.5$ D. strength is required.

The lens grinder's equation, adapted for computing diopter strength in water is

$$D_w=\left(\frac{n_g}{n_w}-1\right)\left(\frac{1}{R_1}+\frac{1}{R_2}\right)$$

n_g = index refraction, glass

n_w = index refraction, water

R_1, R_2 = radii curvature of the lens surfaces

The strongest tool readily available for grinding was $\frac{1,000}{26.5}$. If this was used to grind both surfaces of a 20 mm. diameter loupe which will restrict spherical and chromatic aberration, it would produce a lens of strength

$$D_w=\left(\frac{1.7}{1.33}-1\right)\left(\frac{1,000}{26.5}+\frac{1,000}{26.5}\right)$$
$$=\left(\frac{0.37}{1.33}\right)\left(\frac{2,000}{26.5}\right)=21 \text{ D.}$$

As can be seen, this falls short of the power desired. For reasons of maximal mechanical support it was decided to employ a planoconvex lens 40 mm. in diameter for the additional dioptric power needed. With reference to Figure 2, its radius of curvature should be where

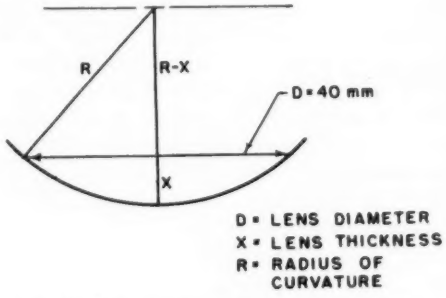


Fig. 2.—Designation used in lens calculation.

D = lens diameter

x = lens thickness

R = radius of curvature

$$R^2=\left(\frac{D}{2}\right)^2+\left(R-x\right)^2$$
$$=400+R^2-2Rx+x^2$$
$$R=\frac{400+x^2}{2x}$$

The available glass blank restricted the lens thickness to 5 mm. Therefore,

$$R=\left(\frac{400+25}{10}\right)=42.5 \text{ mm.}$$
$$D_w=\left(\frac{0.37}{1.33}\right)\left(\frac{1,000}{42.5}\right)=6.5 \text{ D.}$$

Since flint glass in air has 2.5 times the strength it has in water, the final lens system produced was as follows:

Fig. 3.—Subject wearing experimental spectacles. Frosted lens over other eye later removed.

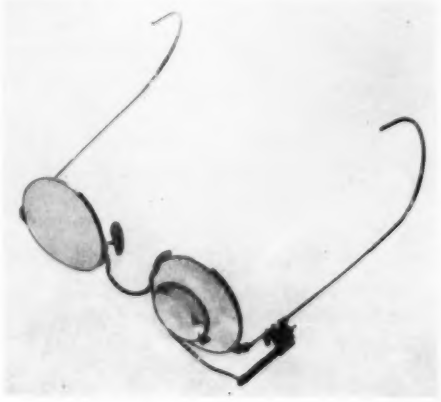
	Water, D.	Air, D.
Planoconvex lens, 40 mm. diameter	6.5	16
Loupe-biconvex, 20 mm. diameter	21.0	52.5
Total	27.5	68.5

Results

The final lens system produced was a combination of a planoconvex lens, 4.0 cm. in diameter, 16 D. in strength, mounted in the right side of a standard gold-filled spectacle frame (Figs. 3 and 4). Superimposed on the fixed lens was a moveable 52 D. biconvex lens, 2.0 cm. in diameter. The smaller lens could be moved farther from the fixed lens, resulting in variations extending from the base 68 D. up to approximately 80+ D. if needed. Actually, as will be seen below, the 68 D. was, if anything, stronger (dioptrically) than was required. All glass had an index of $n = 1.7$. The left eye was covered with a frosted lens (later changed to a clear lens). The total weight was 46 gm.*

Preliminary tests were performed in a swimming pool† where an underwater viewing window mounted in one wall was available. Four subjects, wearing the lens system at the prescribed distance while submerged, were able to see the 6/6 (20/20) line of a standard Snellen distance chart when it was held at varying distances in the air outside the window, ranging from less than 35 cm. to 2.7 m. (the maximum available). The near vision as tested by the Lebensohn near-vision chart was 35/35 (14/14) when held at the standard distance of 35 cm. from the window. The consensus was that the vision of all subjects was definitely improved when a −6 D. crown-glass ($n = 1.5$) lens was held in front of the 68 D. system, indicating that our lens system was

Fig. 4.—Close-up view of base lens and superimposed loupe on moveable arm, later fixed on quadrapod structure.



* The lens system was made by Messrs. Wm. H. Price, Opticians, Bethlehem, Pa.

† Made available by Mr. E. T. Hall, Headmaster, and Colonel S. A. Ward, Athletic Director, the Hill School, Pottstown, Pa.

3 to 4 D. (in air) too strong, calculated thus:

A crown glass has 3.9 times the strength in air that it has in water, and a flint-glass lens has 2.5 times the strength in air that it has in water. It follows, therefore:

$$-6 \text{ D. lens (crown glass) in air} = \frac{9}{3.9} = 1.5 \text{ D. in } H_2O$$

$$-4 \text{ D. lens (flint glass) in air} = \frac{4}{2.5} = 1.5 \text{ D. in } H_2O$$

Thus the optimal underwater dioptric strength of the lens system was found to be 26.0 D. instead of the 27.5 D. originally calculated. Therefore, the 16 D. flint-glass lens (air) was changed to 12 D. (air).

When this was done and the system was tested elsewhere, visual acuity was 6/6 (20/20) and 35/35 (14/14). The lens system was permanently mounted, leaving a small space between lenses to avoid air-bubble formation due to capillary attraction. The field of vision was estimated to be approximately 10 degrees in all directions from fixation.

Comment

Why did the original theoretical calculation vary from the ideal lens-system strength found when actually tested? It may be that the assumptions and the calculations were incorrect. The convergence of light rays by the crystalline lens in the eye was ignored in making the calculation. The effect of this would be to make the over-all optical system too strong. It was convenient to correct this error by testing the subjects with negative crown-glass lenses. It may have been that the human anatomical lens has a different refractive index in vivo than has been previously ascribed to it. There is some evidence on this point.[1] Indeed, it may be that the technique of eliminating corneal refraction by submersion (this could be accomplished in the laboratory by means of a fluid-filled goggle type apparatus) might be employed to investigate the refractory properties of the anatomical lens in the normal eye and other intraocular tissues (as in aphakia).

Conclusions

1. A +64.5 D. (in air) lens system will permit the submerged human eye placed 7.5 cm. from a clear window to see into air with an acuity of 6/6 (20/20) for distance and 35/35 (14/14) for near vision.

2. The field of vision under these circumstances is approximately 20 degrees.

3. The range of accommodation, as measured from the window, extends from 0 to 6 meters.

Mr. R. F. Gray, who assisted in the design of the problem, and Lt. Cmdr. M. G. Webb, both of the staff of the Aviation Medical Acceleration Laboratory, served as principal subjects in all phases of the experiments.

619 Main St., Bethlehem, Pa.

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Studies of the Irritating Action of Methylcellulose

T. C. FLEMING, M.A.; D. L. MERRILL, M.S., Fort Worth, Texas, and LOUIS J. GIRARD, M.D., Houston, Texas

Methylcellulose,* which has been included as a vehicle in many ophthalmic preparations since 1945, is a water-soluble cellulose ether with a high degree of purity and uniformity. Solutions of methylcellulose have cohesive and emollient properties, considerable clarity, and a refractive index similar to that of the cornea. Such solutions are stable in a pH range which is tolerated by the eye and are unaffected by light or aging. When ophthalmic drugs contain methylcellulose, their activity is increased and their action prolonged.[1,2]

In 1945, Swan[3] studied the effects of methylcellulose on the ocular tissues of rabbit eyes. There was no biomicroscopic or histologic evidence of injury. Animal experiments also failed to reveal any inflammatory reaction after subconjunctival injections. However, after intraocular injections, Swan found that 0.1 ml. of a 1.0% solution of methylcellulose produced a mild iridocyclitis.

The present paper is a report of further studies of methylcellulose in relation to irritation, hypersensitiveness, and its outflow from the anterior chamber of rabbit eyes.

Experiments and Results

Effect of Methylcellulose on Subcutaneous Tissues.—In order to study the irritating effects of methylcellulose on subcutaneous tissues, an area on the back of certain albino rabbits was selected as the site of the injection and shaved. Fourteen injections were made at intervals of 48 hours. Each injection consisted of 0.1 ml. of a 0.5% solution of methylcellulose. During a four-week observation period, there was no evidence of irritation.

Effect of Methylcellulose on Tissue Culture.—In studying the irritating effects of methylcellulose on tissue cultures, human conjunctival and corneal epithelial tissues were used. These tissues were grown in Eagles' Medium 4, to which 20% mixed human serum was added. The tissues were cut into 1 mm. sections and placed in clots on hanging drop slides containing check plasma, thrombin (1,000 units), and 500 units each of penicillin and dihydrostreptomycin. A 0.5% solution of methylcellulose was used as an inoculum. The tissues were observed every 24 hours for five days. No toxic or irritating effects were noted, and normal growth was obtained on all cultures.

According to Evans and his associates,[5] the addition of a 0.5% solution of methylcellulose 4,000 C. P. S. to tissue-culture medium has a positive effect on the proliferation of cells.

Hypersensitivity Studies.—In the hypersensitivity studies four guinea pigs, weighing 280 to 350 gm., were used. Two sensitizing injections, consisting of 0.1 ml. of a freshly prepared 0.5% solution of methylcellulose in distilled water, were given subcutaneously at 24-hour intervals. A No. 22 gauge hypodermic needle was used.

On the 15th day after the second sensitizing dose, 0.5 ml. of a 0.5% solution of methylcellulose was injected intracardially. No symptoms of anaphylaxis or hypersensitivity were evident. On killing two of the animals, gross examination of the intestines, blood, stomach, and liver revealed no

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From the Department of Ophthalmology, Baylor University College of Medicine, Houston, Texas, and the Research Department, Alcon Laboratories, Inc., Fort Worth, Texas.

* Methylcellulose was obtained from Dow Chemical Corporation.

congestion, hemorrhage, or emphysema of the lungs.

The Effects of Methylcellulose Combined with Salt Solutions.—An injection of 0.1 ml. of a sterile 0.5% solution of methylcellulose, rendered isotonic with 0.9% sodium chloride, was given into the anterior chamber of one eye of each of seven rabbits. A very mild iridocyclitis ensued. The injection of a 0.9% solution of sodium chloride into the anterior chamber of the opposite eye resulted in a mild iritis. All observations were determined by means of biomicroscopy. Extreme care was taken in order to minimize traumatic irritation resulting from the injections into the anterior chamber.

Because of the mild iritis produced by the 0.9% sodium chloride solution alone, it was believed that a change in the ionic concentration of the aqueous might have produced the mild iridocyclitic condition. Therefore, further intraocular studies were made with use of a balanced salt solution, developed by Hanks,[6] in place of the sodium chloride solution. One eye of each of five animals received an injection of 0.1 ml. of a 0.5% solution of methylcellulose in Hanks' balanced salt solution and the other eye, an equal amount of the balanced salt solution containing no methylcellulose. Upon close examination with the slit lamp no indication of iridocyclitis developed in the control eyes or in the eyes into which methylcellulose in balanced salt solution was injected. Trauma produced by penetration of the needle into the cornea is inherent and was considered in the examination.

Outflow of Methylcellulose from the Anterior Chamber.—In order to determine if methylcellulose would flow out through the normal outflow channels of the eye, qualitative tests were made on the aqueous. Five animals received intraocular injections of 0.1 ml. of a 0.5% methylcellulose solution. On five consecutive days, the aqueous of one of each of the five animals was removed by paracentesis. A qualitative test for the presence of methylcellulose in the aqueous of each of the five animals was performed using anthrone dye,[7] which develops a specific color reaction when combined with methylcellulose. The aqueous from the first three animals gave a positive reaction, but negative results were obtained in the last two animals. Therefore, methylcellulose was present in the anterior chamber of the rabbit eyes for 72 hours after injection but was completely eliminated by the fourth day.

Study of Foreign Substance Reactions.—Extraneous matter implanted within surgical wounds constitutes a foreign substance and, as such, stimulates varying degrees of proliferative tissue reaction. Although mild proliferative foreign-body reaction is of minor concern to the general surgeon, it can be of major significance to the ophthalmologist, particularly in regard to filtering operations for glaucoma.

Talbot and Christensen [8] have shown recently by means of polarized light that two out of three eyes enucleated in the northwestern part of the United States, with a history of previous intraocular surgery, show a significant amount of foreign-body contamination. These investigators indicated that some of the sources of contamination in the operating room are sponges, gloves (talc), drops, and irrigating fluids. In order to eliminate the possibility of methylcellulose causing a foreign-substance reaction of this nature, intraocular studies in animal eyes were initiated.

Three albino rabbits with no previous history of eye surgery were given injections in the following manner. The right eye was given an injection of 0.1 ml. of a 0.5% solution of methylcellulose in balanced salt solution. As a control, the other eye was given an injection of 0.1 ml. of the balanced salt solution. The solutions were prepared by sterile filtration using a sintered-glass filter. The material coming into contact with the solutions to be injected was lint-free in order to assure that the materials to be injected did not cause a foreign-substance reaction by contaminating the test solutions with lint. Ten days after the injections the eyes were removed, after killing the ani-

mals, and the tissues were examined microscopically using polarized light. The results indicated that there were no contaminating foreign substances in either the control eye or the eye into which the methylcellulose was injected.

Conclusions

1. Subcutaneous injections of methylcellulose were found to be nonirritative over a 28-day period when injected into albino rabbits.

2. Tissue-culture studies on human conjunctival and corneal epithelium showed no evidence of inhibition of cellular growth or toxic effects when subjected to a 0.5% solution of methylcellulose.

3. Solutions of methylcellulose did not produce hypersensitivity or anaphylactoid reactions in guinea pigs.

4. Intraocular injections of methylcellulose prepared in a balanced salt solution gave no indications of producing an iridocyclitis, but 0.9% solutions of sodium chloride caused a mild iritis, and injection of methylcellulose combined with sodium chloride produced a mild iridocyclitis. It was, therefore, concluded that the sodium chloride solution rather than the methylcellulose was responsible for the adverse reactions.

5. Qualitative tests indicate that methylcellulose was removed from the anterior chamber by physiologic processes.

6. Microscopic examination using polarized light of animal-eye tissue subjected to methylcellulose gave no evidence of a foreign-substance reaction in the tissues.

Mrs. Alberta Renick and Mrs. Ruby Zellers gave technical assistance.

Hermann Professional Building, Texas Medical Center, Houston 25, Texas (Dr. Girard).

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Ocular Effects of Endotoxin

R. Z. LEVENE, M.D., and G. M. BREININ, M.D., New York

The term endotoxin is used to designate the relatively homogenous group of toxic substances which exist as polysaccharide-protein-lipid complexes in Gram-negative micro-organisms.[38] Lysates of Gram-positive hemolytic streptococci also possess endotoxic properties.[36] Considerable confusion has existed as a result of the variety of names given to these substances by different investigators. They have been known as toxic antigens, polysaccharide toxins, Boivin antigens, or Shwartzman-active toxins. Two important features of these substances are their ubiquity as contaminants and their biologic potency. The active agent in fever or nonspecific-protein therapy is endotoxin.[8] Their biological effects include profound vasomotor disturbances, alterations in the white cell and platelet counts, metabolic alterations, tumor necrosis, and the Shwartzman reaction. With repeated doses there is a rapid appearance of a state of nonspecific resistance or tolerance against further endotoxin effects.

A review of the ophthalmic literature has yielded many examples of ocular effects of endotoxin in the normal eye, although in most cases the nature of the active agent was not known. The most comprehensive study was made in 1942, by Ayo,[1-3] who demonstrated that all bacterial filtrates capable of eliciting an ocular Shwartzman reaction could produce an ocular inflammation after a single systemic injection. He suggested the term toxic ocular reaction for this inflammation. In the present study, the ocular effects of endotoxin in the normal eye are subjected to further investigation.

In the diseased eye, the clinical effects of endotoxin are well documented. They exemplify the so-called focal reaction, an enhanced susceptibility of diseased tissue to endotoxin effects.[43]

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Department of Ophthalmology, New York University, Bellevue Medical Center.

Method

Escherichia coli endotoxin was obtained from Difco Laboratories, where it was prepared by the Boivin method.[10] It was stored at 7 C, and fresh solutions were prepared for each experiment with pyrogen-free saline. Periodically these solutions were tested for sterility on blood-agar media. No growth was observed. Endotoxin was administered by ear vein in a volume of 1 cc. Compound 5-hydroxytryptamine creatinine sulfate (5-HT) was obtained from Abbott Laboratories, and Compound 48/80, a mixture of polymers obtained by condensing alkophenylalkylamine with formaldehyde, was obtained from Burroughs Wellcome & Company, Inc. All substances were shown to be free of endotoxin contamination by the absence of a pyrogen effect in rabbits. The glassware was prepared by soaking in hot Alconox, rinsing in pyrogen-free fluid, autoclaving, and rerinsing just before use.

Young albino rabbits, weighing from 1,000 to 1,500 gm., and adult albino rabbits, weighing from 2,500 to 3,500 gm., were used. Some animals were used twice, allowing an interval of at least three weeks between experiments.

In most cases, examination for ocular inflammation was done with a pen-light. Some rabbits were followed by slit lamp for aqueous flare and cells.

The temperature was determined with a subcutaneous needle-probe attached to a telethermometer and was recorded to the nearest 0.25 degree F.

Tonometry was done on the restrained conscious animal with topical 0.5% buffered isotonic tetracaine anesthesia. Two drops

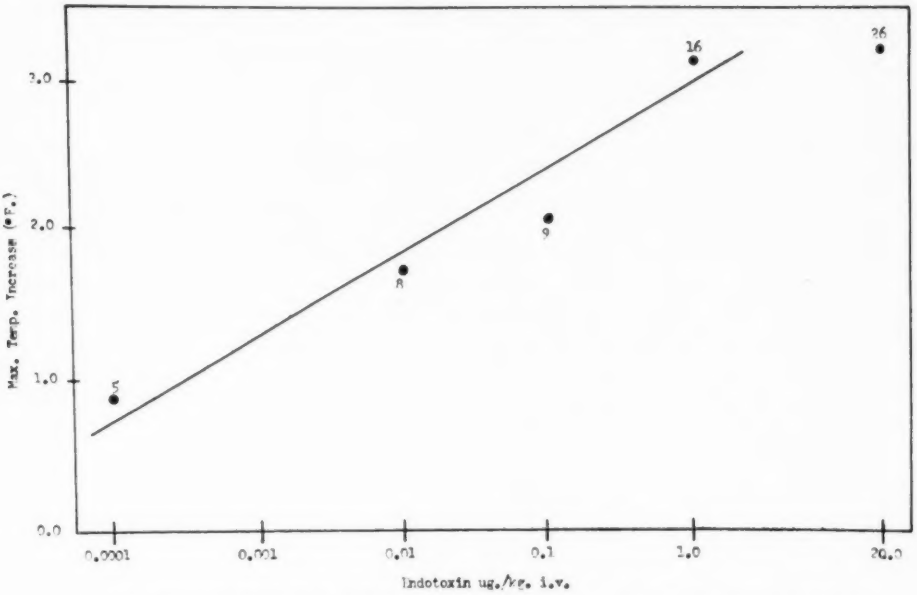

Fig. 1.—Pyrogen effect of E. coli endotoxin in young albino rabbits. The mean values are plotted, and the number of animals per group is indicated.

were instilled, and in 20 to 30 seconds the eyeball was rinsed with warm isotonic saline. The Schiøtz tonometer was used, and the reading was recorded to the nearest one-half scale unit.

In vitro perfusion was done according to the technique of Becker.[5] The perfusion pressure was 20 mm. mercury. The value for the facility of outflow was corrected for body temperature. Animals were killed by

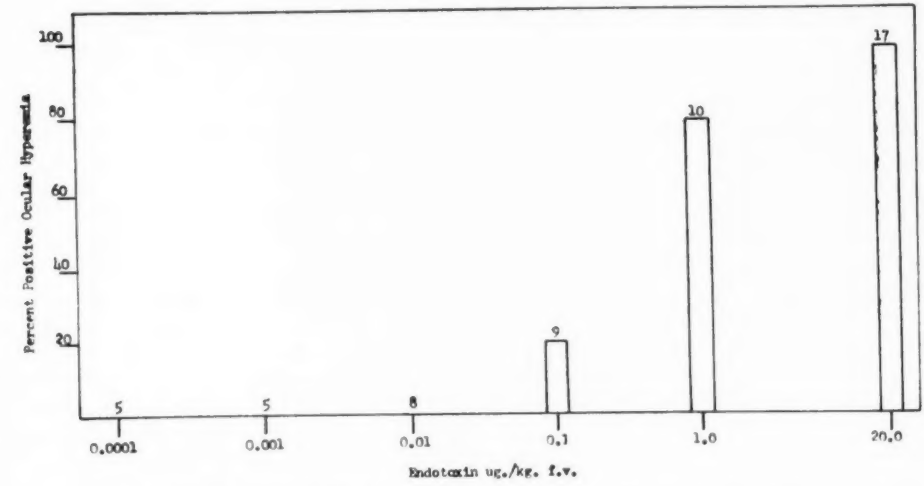

Fig. 2.—Ocular hyperemic effect of E. coli endotoxin in young albino rabbits. The number of animals in each group is indicated.

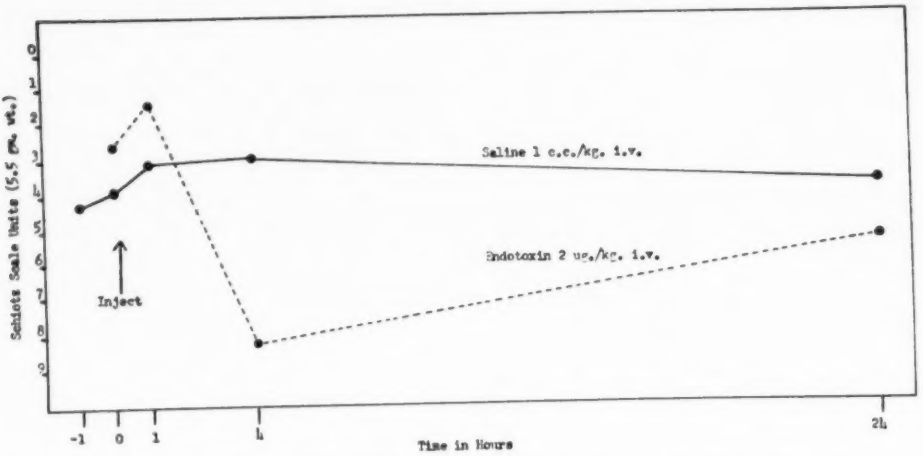

Fig. 3.—Effect of E. coli endotoxin on the intraocular tension in adult albino rabbits. Each point is the mean of 24 eyes of 12 rabbits.

decapitation; the eyeballs were enucleated within minutes and used immediately.

For histologic study, the enucleated globes were fixed in 10% formalin, sectioned in paraffin, and stained with hematoxylin and eosin.

Results

Pyrogen Effect.—The pyrogen effect, a sensitive frequently used indicator of endotoxin effects, was recorded as a base line for comparison with the ocular effect. Figure 1 illustrates the approximately logarithmic dose-effect relationship up to 1.0µg. per kilogram. In 23 controls receiving pyrogen-free saline, the mean temperature increment (± standard deviation of the series) was 0.75±0.32 F. Thus, a temperature increase in a single rabbit, equal to or greater than 1.5 F is significant ($P<0.05$). The corresponding threshold endotoxin dose is 0.0024µg. per kilogram. These results are similar to those of Westphal.[41]

Ocular Inflammation.—The eyes were observed periodically over the first 6 hours and then at 24 hours after intravenous endotoxin administration. The findings were similar to those described by Ayo.[1,3] They include hyperemia of the superficial iris capillaries and of the palpebral and bulbar conjunctival vessels, miosis, photophobia, lacrimation, and increased coagulation of the removed aqueous. An aqueous protein flare was noted in 95% of the animals, and an occasional aqueous cell was seen in less than 5%. There was an initial delay in the development of the inflammation of 15 to 30 minutes. The peak intensity occurred between ½ to 5 hours, and at 24 hours, only those animals receiving large doses showed minimal residual inflammation. Figure 2 illustrates the dose-effect relationship. The threshold dose for ocular hyperemia is approximately 0.1µg. per kilogram, 40 times the threshold pyrogen dose. Vascular effects of endotoxin are widespread, and it would be of interest to know whether a similar inflammation can be produced in other blood-serous fluid barriers.

Intraocular Tension.—Figure 3 compares the effect of endotoxin and saline on the intraocular tension. The endotoxin reaction is biphasic, with a short rise and a subsequent prolonged hypotony. The mean maximum decrease from preinjection level is 5.5 Schiøtz-scale units. Twenty of the twenty-four animals had a drop greater than 3 scale units, while three showed a decrease greater than 10 scale units. None of the saline animals had a fluctuation greater than 3 scale units. All the animals receiving endotoxin showed an ocular inflammation,

TABLE 1.—*Facility of Outflow in Adult Rabbits After Endotoxin* *

Method	Saline †	Endotoxin ‡
Perfusion in vitro	0.33±.02	0.33±.02

*Results expressed as mean of 16 to 18 eyes ± standard error of the mean.

† Saline, 1 cc. I. V. 5 hr. before rabbits were killed.

‡ Endotoxin, 20 μg. per kilogram I. V. 5 hr. before rabbits were killed.

with the exception of the four that had a minimal tension decrease. Thus, a significant tension decrease is associated with an ocular inflammation.

Table 1 compares the effect of endotoxin and saline on the in vitro facility of aqueous outflow. There is no increase in the facility of outflow after administration of endotoxin.

Pathology.—The pathologic effects following a single intravenous injection of 1μg., 20μg., or 200μg. per kilogram of endotoxin were studied in rabbits after intervals of 2, 5, and 24 hours. The changes consisted of edema, hemoconcentration and hemorrhage of the anterior uvea, particularly the anterior ciliary processes (Fig. 4), and intra- and extravascular polymorphonuclear infiltration of the uvea, retina, and chamber angle (Figs. 5-8). Leukocytic infiltration was not limited to intraocular structures but was also noted extraocularly in the subconjunctival tissues and extraocular muscles (Fig. 9). No difference was noted between young and adult animals receiving the same total dose. Vascular changes were marked in all animals after the 200μg. dose, minimal or absent after 20μg., and completely absent after 1μg. The threshold dose for pathologic vascular changes is thus much greater than that for in vivo ocular effects. Leukocytic infiltration, a much more sensitive indicator of endotoxin, was also present after 1μg. per kilogram. All changes were most marked at five hours. Ayo [2] had noted leukocytic infiltration of uvea and retina several hours after administration of the Shwartzman toxins.

In other tissues of animals that have received a single lethal dose of endotoxin, Thomas [38] has noted a paucity of anatomical changes in relation to the violence of the systemic reaction. In the rabbit one may find punctate hemorrhages, small areas of acute cellular necrosis, or small thrombi in various body organs.

Pretreatment with Cortisone or Compound 48/80.—Table 2 demonstrates the effect of cortisone pretreatment. There was a complete inhibition of the in vivo ocular actions of a 2μg. per kilogram endotoxin injection but only a partial inhibition after 20μg. per kilogram. Leukocytic infiltration of the tissues was not inhibited. There was a moderate inhibition of the pyrogen effect

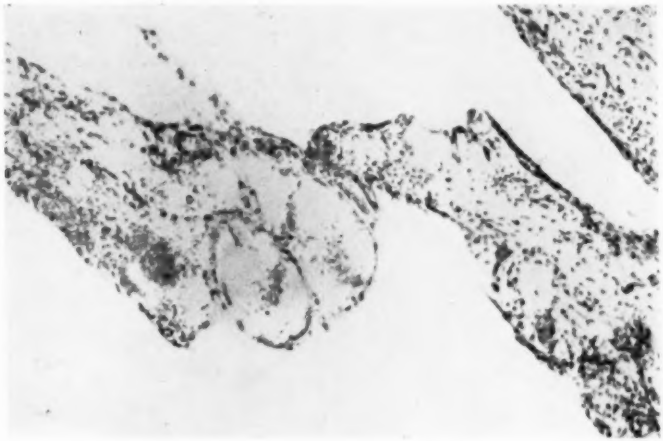

Fig. 4.—Ciliary process with hemorrhage, edema, and Greeff cysts. Albino rabbit, 1,200 gm., five hours after endotoxin 200μg. per kilogram I. V.

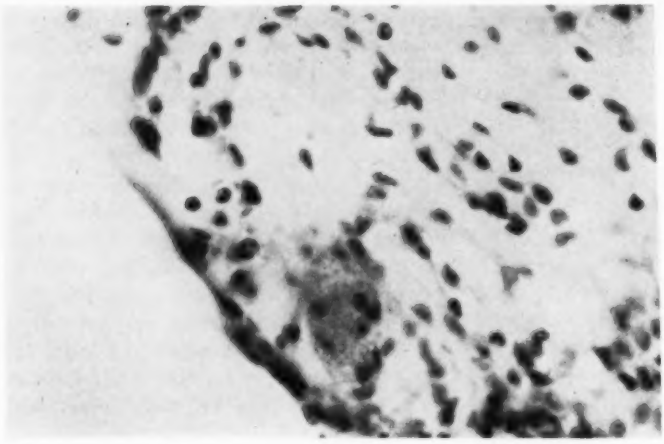

Fig. 5.—Ciliary process of Figure 4 under greater magnification. Leukocytic infiltration.

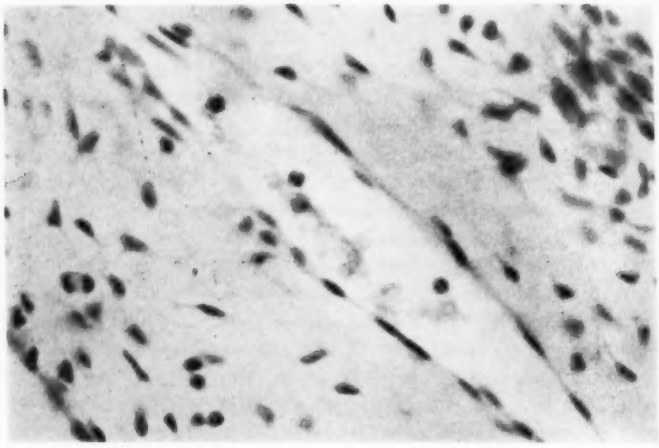

Fig. 6.—Leukocytes in iris vessel. Albino rabbit, 1,100 gm., 24 hr. after endotoxin 200μg. per kilogram I. V.

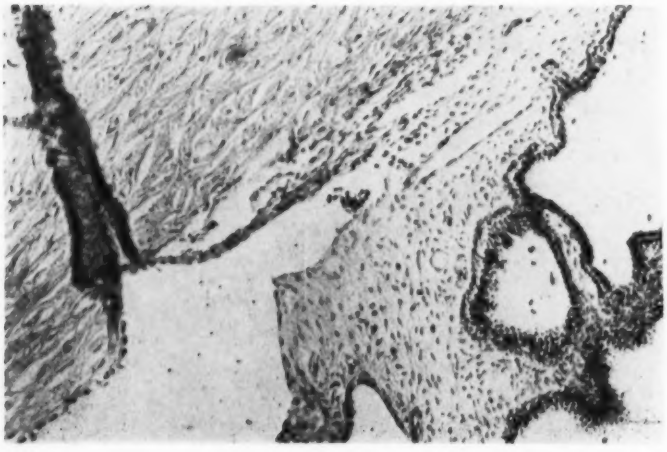

Fig. 7.—Leukocytes in angle of anterior chamber. Albino rabbit, 1,250 gm., 24 hr. after endotoxin 200μg. per kilogram I. V.

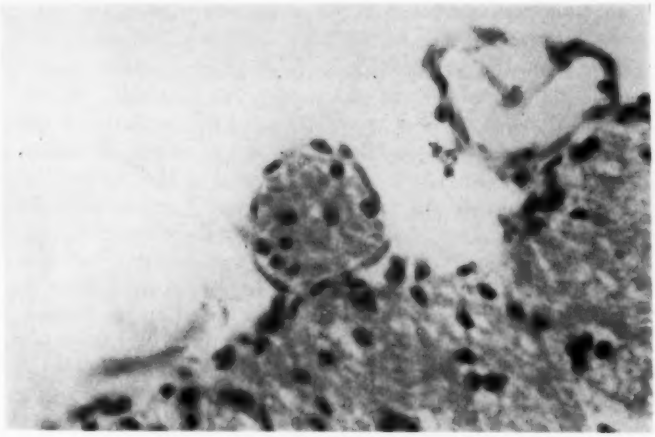

Fig. 8.—Leukocytes in retinal vessel. Albino rabbit, 1,300 gm., four and one-half hours after endotoxin 200μg. per kilogram I. V.

TABLE 2.—*Effect of Cortisone Pretreatment* in Endotoxin-Treated Rabbits*

Endotoxin	Temperature Increase	Ocular Hyperemia	Ocular Tension Decrease
2 μg./kg. I. V.	1.68 F Equiv. to 0.005μg. Endotoxin/kg. (8) †	Complete inhibition in 92% (12)	None (8)
20 μg/kg. I. V.	2.52 F Equiv. to 0.14μg. Endotoxin/kg. (8)	Partial inhibition in 45% (11)	

* Cortisone 10 mg. per kilogram i. m. for three days.

† Number of animals given in parentheses. All were young rabbits except those tested for tension decrease.

in both cases. The effects of cortisone on other actions of endotoxin are variable, depending on the endotoxin action in question and the dose relationships.[8,38]

Pretreatment in rats for several days with Compound 48/80, a histamine and 5-HT releaser, protected against the general shock-like effects of endotoxin.[39] Eight young rabbits were pretreated with Compound 48/80 for four days with increasing i. v. doses from 0.5 mg. per kilogram to 1.5 mg. per kilogram. This pretreatment did not inhibit the ocular inflammation of a 1μg. per kilogram endotoxin injection. Compound 48/80 also does not minimize the ocular inflammatory effect of trauma.[42]

Tolerance.—Five young rabbits were given endotoxin, 5μg. per kilogram every three days for five doses. The ocular inflammation after the second dose was much less marked than after the initial injection, and after the fourth injection no ocular in-

Fig. 9.—Leukocytic infiltration in extraocular muscle. Albino rabbit, 1,300 gm., 24 hr. after endotoxin 200μg. per kilogram I. V.

flammation was observed. These results are similar to those of Ayo.[1]

Effects of Epinephrine.—Thomas et. al.[39] have reported that epinephrine injected locally in the abdominal skin of rabbits produces extensive lesions of hemorrhagic necrosis when injected in the presence of endotoxin, whether the latter is given by vein or locally in a mixture with epinephrine. Furthermore, 5-HT in the presence of epinephrine elicits reactions of vascular injury similar to those produced by endotoxin in the presence of epinephrine. However, Ayo[2] has reported that a retrobulbar injection of epinephrine inhibits the toxic ocular reaction for the first few hours.

Epinephrine in doses of 25μg. to 250μg. was injected into the subconjunctival tissue or vitreous of the eye in the presence of endotoxin or 5-HT. Endotoxin in doses of 10μg. to 100μg. was given either by vein or locally as a mixture with the epinephrine. Compound 5-HT in similar amounts was only given locally. No lesion resembling that described in the skin was noted, although control abdominal skin lesions were positive. For the first few hours epinephrine inhibited the inflammatory effects of endotoxin, while after 24 hours epinephrine slightly augmented them. This biphasic effect of epinephrine can be seen after local instillation of the drug itself.[17] The skin and the eye respond in a different manner to a mixture of endotoxin or 5-HT and epinephrine.

Comment

Endotoxin, in small amounts, can produce an ocular inflammation with an associated breakdown of the blood-aqueous barrier and a biphasic alteration in intraocular tension. As the tension is a function of many factors, one cannot identify with certainty the mechanisms involved in these changes. The initial rise is probably a result of the increased vascular volume associated with vascular dilation. As there is no increase in the aqueous outflow facility, the subsequent prolonged hypotony is probably a result of a decreased net formation of aqueous by the ciliary body.

Ocular effects of endotoxin in normal animal eyes have been observed periodically by other investigators, although in most cases the nature of the active agent was not known. The detailed study by Ayo has been noted. Ocular inflammatory and pathologic effects, similar to those described above, were noted in the normal rabbit eye by von Szily[37] after the administration of various pyrogen-protein solutions, by Rosenow and Nickel[32] after the injection of killed streptococci, and by Berens and Nilson[9] after the injection of coliform bacteria. A biphasic pressure response with prolonged hypotony and similar ocular pathology were noted by Poos[30] in normal rabbit eyes after the administration of various salt solutions. Endotoxin contamination was undoubtedly present.

In normal human eyes, a clinical ocular inflammation after administration of endotoxin is rare. In a report by Hench[21] on 2500 patients receiving fever therapy, there was only one case of an ocular inflammation in a previously normal eye. This difference in ocular effects may be a result of a species difference. Ayo[1] has demonstrated that per kilogram dose it is more difficult to elicit a toxic ocular inflammation in rhesus monkeys and guinea pigs than in rabbits. Again, the use of a dose greater than the threshold for a clinical ocular inflammation is probably rare, as satisfactory systemic reactions can be obtained with lower doses. However, subclinical inflammatory changes cannot be ruled out.

In diseased human eyes, the initial increase of an existing ocular inflammation after endotoxin therapy is well known.[43] In 1938, Bellows et al.[7] reported a prolonged tension drop for 12-24 hours in glaucomatous patients after administration of intravenous sorbitol, while de Roetth,[31] repeating the investigation in 1954, reported a moderate decrease in ocular tension for two to three hours. An endotoxin contamination was very likely present in the earlier experiment. A decrease in intraocular tension has

been noted in glaucomatous patients receiving nonspecific-protein therapy, although a marked tension decrease in the absence of intraocular irritation was rare.[28]

The pyrogen effect of endotoxin-contaminated solutions is well known, but their capability of producing ocular effects in the normal eye has not been fully appreciated. While the strict use of pyrogen-free solutions has eliminated the problem of contamination in humans, the exclusion of endotoxin contamination in animal experiments has not been as complete. Sterilization by autoclave or Seitz filtration decreases but does not exclude endotoxin activity. Apart from contamination of fluids, endotoxin can be present in various chemical substances, particularly those that favor bacterial growth. In a separate investigation on the effects of papain,[25] endotoxin contamination of this enzyme was found.

The ocular effects of endotoxin are not specific. Similar inflammatory, biphasic tension, and pathologic effects have been produced by local trauma,[13,23,24,28,29] cervical sympathectomy or ganglionectomy,[14,22,26,27,29] topical or subconjunctival injection of eserine,[15,29] pilocarpine,[4,29] di-isopropyl fluorophosphate (D. F. P.),[33,34] or epinephrine.[6,16,29] In some cases, depending on the time of observation, only one tension phase has been noted. A decreased aqueous formation occurs during the hypotonic phase.[4,6,20,26,27] A local histamine injection has produced similar results without the leukocytic infiltration.[19,40] Epinephrine has an early inhibitory effect on the inflammation after local trauma,[17,28] topical application of D. F. P.,[33] or histamine.[35] The similarity in effects produced by a wide variety of ocular insults suggests a final common ocular mechanism. The nature of this mechanism is unknown, although the release of histamine or a histamine-like substance has been suggested.[18] Direct conclusive evidence for the release of histamine and its role in ocular inflammation has not been presented.

The development of endotoxin tolerance may well be an important factor in the therapeutic efficacy of nonspecific-protein therapy. Although it is the usual clinical procedure to maintain a pyrogen effect by the gradual increase of successive doses, the normal course of four to six injections will produce a state of tolerance to the lower doses. Furthermore, beneficial results have been reported without appreciable fever.[11,12] Long-term beneficial effects have been reported after long-term treatment with streptococcal vaccines,[43,44] preparations that possess endotoxic properties.[36] While specific desensitization has been emphasized as the rationale of this treatment, the concomitant development of a nonspecific endotoxin tolerance is highly likely and merits further attention.

Summary

The effects of endotoxin on the normal rabbit eye have been investigated. Endotoxin in small amounts can produce ocular inflammation with an associated breakdown of the blood-aqueous barrier and a biphasic alteration in intraocular tension. There is no increase in aqueous outflow facility during the prolonged hypotonic phase, suggesting a decreased net aqueous formation. The threshold dose for the ocular effects is approximately 40 times that for the pyrogen effect. The threshold dose for vascular pathologic changes of the anterior uvea is much greater than that for the in vivo effects. Leukocytic infiltration is a much more sensitive indicator of endotoxin. Pretreatment with cortisone completely inhibits the in vivo ocular effects of 2μg. per kilogram of endotoxin. Pretreatment with Compound 48/80 has no effect on the in vivo effects of a 1μg. per kilogram dose. Tolerance to the ocular inflammatory effect can be quickly developed. Local epinephrine has a biphasic action on the ocular inflammation of endotoxin. The physiologic and pathologic effects of endotoxin are not specific. They can be produced by a variety of ocular insults, suggesting a final common ocular mechanism. The ubiquity of endotoxin as a contaminant and the importance of recognizing its ocular

effects in the normal eye are stressed. The possible role of endotoxin tolerance in the therapeutic efficacy of nonspecific-protein therapy is discussed.

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The Depth of Focus of the Eye

J. THEODORE SCHWARTZ, M.D., and KENNETH N. OGLE, Ph.D., Rochester, Minn.

The depth of focus of the eye is of importance to the ophthalmologist primarily as it relates to visual acuity. For example, when determining the range of clear vision of an early presbyope at near, the examiner determines the range of distances from the eye within which the patient can clearly read print of a given size. Depth of focus determines part of this range. The depth of focus bears consideration in all testing of visual acuity as it relates to refraction. This is particularly true when the refractive correction is being determined for distant vision in the usual subjective manner. Depth of focus very likely plays a marked role also when miotics, such as DFP (di-isopropyl fluorophosphate), are used therapeutically in cases of convergence excess. This and other practical considerations are treated later.

There is no absolute value for the depth of focus, for it varies greatly with test conditions as well as with the criterion used in its determination. This paper is a report of data obtained on the depth of focus of the human eye by means of controlled experimental conditions and the specific criterion of loss of visual resolution.

Figure 1 illustrates the quantities used in the specification of depth of focus. Assume that the eye is fixated on point C on the visual axis and that the state of accommodation remains constant for the stimulus to accommodation given by that point. Now if a *test* target is moved along the axis, nearer to or farther from the eye than point C, the image falling on the retina becomes blurred because the real image of the test target actually lies in front of or behind the retina. Thus, the out-of-focus image of a point is a blur disc on the retina. For a given perceptual criterion of limiting focus there would be a maximal allowable blur. Corresponding to the maximally permitted blur disc would be a *proximal* position, P, and a *distal* position, D, of the test target, at distances p and d from the eye, respectively. The total *depth of focus* (in diopters) is then defined as follows: depth of focus $= 1/p - 1/d$ (when p and d are expressed in meters). The actual spatial interval between P and D is called the "depth of field."

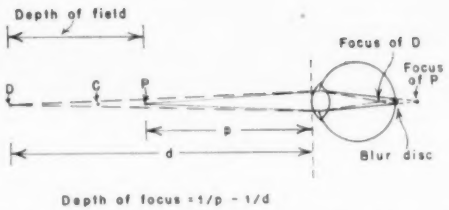

Fig. 1.—The quantities used to define depth of field and depth of focus of the eye, corresponding to a maximal tolerable blur of the retinal image.

For visual objects consisting of a pattern of light and dark areas, the out-of-focus imagery would result in a complicated overlap of blur circles and in a complex pattern of light-intensity distribution on the retina. As these become increasingly more out of focus, the contrasts would be reduced and contours would lose their sharpness. Because of the nature of the aberrations of the eye and the existence of small irregular astigmatic errors, the effect of out-of-focus imagery would be more complex than that

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Fellow in Ophthalmology (Dr. Schwartz) and Section of Biophysics (Dr. Ogle), Mayo Foundation. The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

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of a centered optical system, such as the camera lens.

It becomes evident, then, that when one attempts to make measurements of depth of focus he must select a particular quality or effect of this out-of-focus imagery as his criterion of visual tolerance. Most of the data reported in the literature are based on the criterion of the least perceptible blurring of the image, namely, those of Ogle,[1] von Bahr,[2] Campbell,[3] and Oshima,[4] to mention more recent investigators. The data obtained in this present report are based on the criterion of deterioration of resolving power with increase of out-of-focus imagery.*

These measurements have been made under carefully controlled conditions, so that only the influence of out-of-focus imagery on visual resolution was being measured. The following factors, all of which have potential influence on depth of focus, were held constant: pupil size, accommodative state, light-adaptation level, spectral distribution, fixation distance, target-exposure time, and target illumination. The following special features were used in this experiment: 1. Normal binocular vision was maintained, while the depth of focus was measured on the right eye only. 2. The checkerboard target was used as the critical visual acuity test chart, first, because its discrimination seems to depend more on visual resolution alone than does that of many other charts that might be used,[6] and, second, because it is easily adaptable to a psychophysical procedure. This chart has been extensively studied by Dimmick [7] and Morris [8] and their co-workers. 3. The angular size of the test target was held constant irrespective of the degree of out-of-focus blur. 4. The test target was exposed for observation for only 1/5 second. This short duration prevented changes in accommodation during the exposure, and, furthermore, it limited voluntary scanning eye movements. 5. Standard psychophysical procedures were used to determine the degree of deterioration of the resolving power.

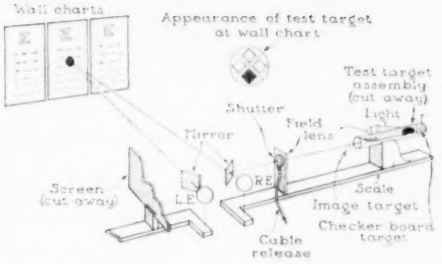

Fig. 2.—A perspective sketch of the instrument used to measure the depth of focus of the eye.

Instrumentation

The basic instrument was a haploscope (Fig. 2) with half-silvered mirrors. The observer looked toward the center of three Snellen wall charts at a viewing distance of 4 meters and fixated the point of intersection of two white threads stretched at oblique axes across a round hole (5 cm. diameter) opening into a black chamber behind. The details of the wall charts provided adequate stimuli for fusion. These charts were illuminated by two banks of fluorescent lamps, and the luminance measured by the Macbeth illuminometer through the mirrors of the haploscope was about 12 millilamberts.

On the right arm of the haploscope, the test target was so arranged that it could be seen at the center of the wall chart by reflection. The checkerboard target † was placed in the end of the target assembly (Fig. 2) and was illuminated by a microscope substage lamp mounted on the side of the housing. The intensity of the test-target illumination could be varied by a rheostat.

* A third possible criterion would be loss of visibility or detectability through complete loss of contrast with background. A fourth criterion would be the minimal stimulus needed to elicit an accommodative change. The first three would depend on perceptual tolerances,[6] while the last would depend on a physiologic tolerance.

† The target used was supplied by Dr. F. L. Dimmick, of the Medical Research Laboratory of the U. S. Naval Submarine Base, New London, Conn.

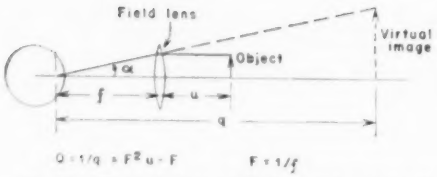

Fig. 3.—The principle of Badal, used to keep the image of a test object a constant angular size.

The test target ‡ was viewed through an achromatic field lens as shown. This field lens was so placed that the second focal point coincided with the entrance pupil of the subject's eye. With this arrangement, based on the Badal optometer principle[9] (Fig. 3), the angular size of the checkerboard image seen by the eye remains constant, irrespective of the degree to which the target is out of focus. Also, by this arrangement the dioptric distance, Q, of this image from the eye has a linear relationship with the actual distance, u, of the target from the field lens of power F, namely, $Q = F^2u - F$.

With the use of a field lens of given power, the arm of the haploscope can be calibrated to read directly in dioptric distance of the image from the eye (Q) for each corresponding position of the target along the arm.

By adding a suitable supplementary lens of low power to the field lens and then relocating the position of the new field lens unit so that the second principal point of the combined field lens system again coincided with the entrance pupil of the eye, the angular magnification of the test target could be changed. By such relocation and recalibration, the angular size of the test target was increased in stepwise fashion from 20/20 up to 20/40 (equivalent Snellen notation). At each different size setting, the image seen by the observer, of course, remained constant at the new size regardless of the degree of blurring.

A shutter was mounted in front of the field lens and was operated by the subject.

A four-button headrest and chin cup were used to support the head of the observer in the instrument. The entire apparatus was carefully adjusted, and the scales were accurately calibrated. The subject's gaze was constantly fixed on the cross threads at the wall chart and, as the test-target unit was moved along the haploscope arm, the image, when exposed, remained in the center of the black hole on the wall chart.

To obtain an accurate record of the size of the entrance pupil during the experiments, an Exacta reflex 35-mm. camera assembly was used with a synchronous electronic flash lamp. This was placed in position between the eye and the field lens in a few seconds whenever pupil photographs were desired. The size of the entrance pupil was measured from the projected image of the film in a microfilm reader, which gave a magnification of 13.5 times.

The checkerboard pattern of the test target was always oriented either up or down in the housing. It was the task of the subject to discriminate properly the up-or-down orientation. By keeping this test detail always in one meridian, any bias or influence of small uncorrected astigmatism in the observer's eye was eliminated. Since the fixation point would be at the center between the four square parts of the test chart, the checkerboard pattern itself would never be seen exactly by the center of the fovea but at a visual angle of about 5 minutes of arc above or below this point.

Procedure

By adjusting the headrest, the head of the observer was accurately positioned with respect to the instrument, so that the right eye was properly centered and located. Preceding the experiment, and with the shutter open, the rheostat controlling the light il-

‡ It was desired to have a test target of specific basic size. In order to avoid a change in definition of the target with resulting invalidation through photoreduction of the original, a real image of desired basic size was formed in front of the target assembly by using a reversed 8-mm. Ciné projection lens. The length of the housing was adjusted to obtain the desired size of the "image target," and the target housing was then locked to maintain the size throughout the present experiment. It is this real image target of specific basic size which was the object or test target in these experiments.

luminating the test target was adjusted by the observer until the background of the test target and that of the wall chart appeared equally bright.

The operator would set the test-target unit at certain positions along the arm of the haploscope. At each position the operator would indicate to the subject when the setting was ready, and the subject then tripped the shutter which exposed the test target, while he fixed his gaze on the distant cross threads. He made the observation and then stated whether he saw the checkerboard "up" or "down." He was forced to guess if uncertain. By trial and error a range of test-target positions was found within which the subject correctly discriminated the orientation of the checkerboard at every exposure. It is this range which determines depth of focus. At the distal and proximal ends of this range, the image became increasingly more blurred and the orientation of the target became more difficult to discriminate. In order to specify appropriate end-points at these proximal and distal blurring regions, the data were collected by the forced-choice, two-category, constant-stimulus method.

Specifically, at either the proximal or distal blurring region, the operator determined a range of settings of the test target by trial and error. At one end of this range the orientation of the target was always reported correctly. At the other end the forced reports of target orientation were equally wrong and right and represented pure guess; therefore, at these settings the target was blurred to a degree which eliminated all true discrimination. This entire range was subdivided by five equally spaced target settings. The test target was then presented 20 times in random order at each of these five settings. During half of these exposures the target was presented in the "up" position, and in the other half in the "down" position. One hundred observations were necessary over the proximal range as well as over the distal range of blur. The number of correct and incorrect responses were determined for each setting of 20 exposures.

For each exposure of the test target, there was a certain probability of correctly guessing the target orientation. Correct guesses were eliminated from the raw data at each setting of 20 exposures, by the relationship $P=10(N-10)$. Here, P equals the percentage of exposures for which the subject was probably able to discriminate truly the details of the checkerboard rather than to guess correctly and N represents the total responses correctly stated.

The values of percentage of true discrimination P for each target setting were plotted on suitable graphs.

Results

Typical sets of data for the "proximal blurring" and "distal blurring" for one observer are shown graphically in Figure 4. The abscissa are the *diopters* of displacement of the image of the test target referred to the dioptric distance of the fixation point at the wall chart. These scale units, then, correspond to the degree of out-of-focus imagery: the "distal blurring" to the right corresponds to the type of blur experienced in uncorrected myopia, and the "proximal blurring" to the left corresponds to the type of blur experienced, for example, by the presbyope for a near object. On the or-

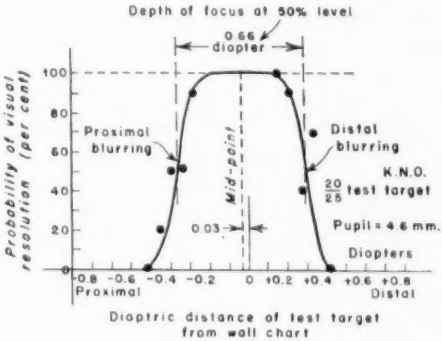

Fig. 4.—Typical data of proximal and distal limits of the depth of focus of the eye, plotted on a linear ordinate scale and showing the ogive curves of the proximal and distal deterioration of visual resolution with increased out-of-focus imagery.

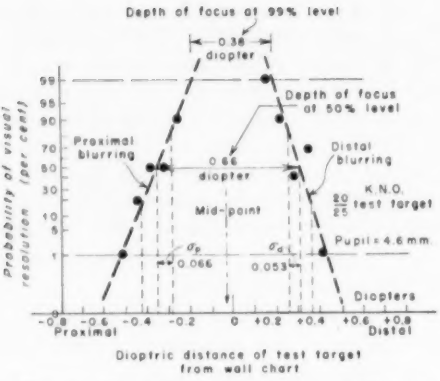

Fig. 5.—The same data as those of Figure 4 plotted on a probability scale as ordinates.

dinates is plotted the per cent probability that the detail of the checkerboard target was truly discriminated and therefore visually resolved. It is interesting to note the rapid deterioration of the ability to discriminate the details of the test chart after a fairly critical degree of blurring of the retinal image has occurred.

In Figure 5 the same data are shown plotted on a probability scale. On the assumption that these probable visual-resolution data are normally distributed, they can be adequately described by straight lines on this type of graph. The lines shown in this graph were fitted to the data points by inspection, although they also may be determined by computation by means of standard statistical procedures. The curves drawn through the data points of Figure 4 were obtained by interpolation from the fitted lines in Figure 5.

The dioptric value corresponding to the 50% level of probable resolution is the most accurate statistic, and this can be found by inspection of the graphic data or by calculation. This represents the level at which the target was probably truly discriminated 50% of the times exposed. The dioptric range between the "proximal" and "distal" points at this 50% level is a measure, and the most accurate measure, of the depth of focus of the eye under the experimental conditions described previously. For the data shown, the depth of focus at this 50% level of probable resolution is 0.66 D. Now we may also *estimate* the depth of focus of the eye at the 99% level of probable visual resolution by placing some reliance on the slopes of the lines that have been fitted to describe the two sets of data. At the 99% level the result will be less accurate than that determined for the 50% level. Nevertheless, the depth of focus at this 99% level is of special interest, since it indicates the range of out-of-focus imagery within which there is no deterioration of the ability to resolve the target pattern. For the data shown, the depth of focus at the 99% level would be estimated as only 0.38 D.

The rate at which the visual resolution deteriorates, after it begins to do so as the out-of-focus blurring is increased, can be expressed by the slope of the line describing the data. The steeper the slope, the more rapid is the deterioration in the visual resolution. It is convenient, however, to express this slope in a reciprocal manner, that is, in terms of the difference in diopters of out-of-focus blurring between two specified levels of probable visual resolution, for example, between the 50% and the 16% level. This quantity, so specified, is equivalent to the standard deviation, σ, of the normal probability frequency distribution. The smaller this standard deviation, the steeper is the slope of the line in the graph and the more rapid is the deterioration of the visual resolution with blurring. For the data illustrated in Figure 5, these values are 0.066 and 0.053 D. for the proximal and distal blurring, respectively.

The midpoint of the depth of focus, according to the analysis of these data for this subject, is 0.03 D. nearer the observer than the actual position of the fixation-point wall charts.

Three subjects were used in the present study, two of whom were essentially emmetropic and nonpresbyopic. The third subject, who was partially presbyopic, used spectacles with the following prescription for the tests: R: $-0.12-0.25\times90$; L: $-0.25-0.25\times105$. In the several experi-

TABLE 1.—*Summary of Depth-of-Focus Measurements of Three Observers Made on Different Days* *

Subject	Sets	Depth of Focus		Rate of Deterioration		Dioptric Displacement		Average Diameter of Pupil (Mm.)
		D_{50}	D_{99}	σ_p	σ_d	Δ_{50}	Δ_{99}	
K. N. O.	1	0.80	0.37	0.070	0.115	−0.05	−0.10	4.8
	2	0.86	0.60	0.085	0.028	−0.04	+0.03	4.8
	3	0.66	0.38	0.065	0.065	−0.03	−0.02	4.7
	Av.	0.78	0.45	0.074	0.069	−0.04	−0.03	4.8
J. T. S.	1	1.11	0.82	0.051	0.072	−0.30	−0.32	4.2
	2	1.02	0.73	0.066	0.054	−0.28	−0.28	3.9
	3	1.01	0.71	0.067	0.067	−0.20	−0.21	3.6
	Av.	1.04	0.75	0.061	0.064	−0.26	−0.27	3.9
E. J. L.	1	0.95	0.62	0.068	0.067	−0.16	−0.16	5.3
	2	1.14	0.86	0.080	0.041	−0.19	−0.14	5.3
	3	0.92	0.55	0.068	0.091	−0.09	−0.12	5.4
	Av.	1.00	0.68	0.072	0.066	−0.15	−0.11	5.3
Group average		0.94	0.63	0.069	0.066	----	----	4.7

* Target size, 20/25; exposure time, 1/5 second; general luminance, 12 millilamberts; all values, except pupil size, in diopters.

ments to be described, three completely separate sets of data were obtained on different days for each experiment.

Typical results for these three observers are shown in Table 1. These were obtained for the checkerboard target, the details of which subtended a visual angle of 1.25 minutes of arc, or a size corresponding to 20/25 Snellen notation. The following values are given: (1) the depth of focus determined at the 50% level of probable visual resolution, D_{50}, and the values estimated at the 99% level, D_{99}; (2) the rate of deterioration of the visual resolution for the proximal and distal blur ranges in terms of the standard deviation of distribution (σ_p and σ_d), and (3) the dioptric displacement of the midpoint of the depth-of-focus range from the dioptric distance of the wall charts, calculated at the 50% and 99% levels (Δ_{50} and Δ_{99}).

These data do not show any correlation between the prevailing size of pupil and the corresponding depth of focus of the three subjects. This finding is probably related to the difference in aberrations among the eyes of the three subjects. It is also interesting to note that the rate of deterioration of visual resolution of the test details with increase of out-of-focus blur is essentially the same for the proximal blurring as for the distal. Because of the theoretical difference in the structure of the caustic surface proximal and distal to the position of "best" focus, a difference might have been anticipated here.

The average value of the prevailing pupil diameter among the three subjects under these experimental conditions was 4.7 mm. By means of a target of a size equivalent to 20/25, the average depth of focus was 0.6 D. at the 99% level of probable visual resolution and about 0.9 D. at the 50% level. It should be kept in mind that these figures do not represent a statistically significant population sample; they are presented here as working values only. They will vary with test conditions.

We shall now report those results showing the variation of depth of focus (1) with change in the angular size of the details of the test target and (2) with change in size of the pupil.

Depth of Focus and Target Size.—The angular size of the checkerboard pattern was changed by adding auxiliary lenses to the field lens as described earlier.

The results of measurements on the depth of focus for one subject for the five target sizes used are summarized in Table 2. The values for depth of focus shown in the Table are the averages of three complete sets obtained on separate days, and, therefore, each represents the analysis of 600 observations. A marked increase is shown in the depth of focus from the 20/20 to the 20/40 test-target sizes. Also the rate at which the probable visual resolution falls off, as given

TABLE 2.—*Summary of Data for One Subject (J. T. S.) for Change in Test-Target Size*

	Size of Test Target				
	20/20	20/25	20/30	20/35	20/40
Mean size of entrance pupil, mm.	3.7	3.9	4.0	3.8	4.0
Depth of focus, 50% level, D.	0.71	1.04	1.71	1.95	2.24
Depth of focus, estimated at 99% level, D.	0.33	0.76	1.31	1.45	1.65
σ for proximal distribution, D.	0.10	0.06	0.10	0.11	0.13
σ for distal distribution, D.	0.08	0.07	0.08	0.10	0.12
Displacement of midpoint, 50% level, D.	−0.25	−0.26	−0.26	−0.27	−0.33
Displacement of midpoint, 99% level, D.	−0.23	−0.27	−0.28	−0.25	−0.32

by the standard deviation, σ, does not seem to vary significantly with the different sizes of the test targets. It is of interest also that for this subject the middle of the depth-of-focus range lies 0.28 D. proximal to the dioptric distance of the fixation point at the wall chart. This was characteristic of all data obtained by this subject. If we assume that this point represents the point at which sharpest imagery would be obtained, that is, the true point conjugate to the retina, then this subject is accommodated about 0.3 D. or the eyes are relatively myopic to the wall charts to that extent. For the other two subjects, this displacement was consistently 0.03 and 0.13 D., respectively, also on the myopic side. These findings are consistent with those already reported for refractive measurements obtained by the method of stigmatoscopy.[10]

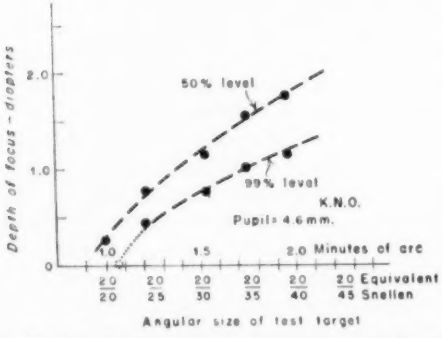

Fig. 6.—Graph of the summary of the depth-of-focus measurements for one subject, for test targets of different angular sizes, determined for the 50% level and estimated at the 99% level of probable visual resolution.

Figure 6 illustrates graphically the results for a second subject (K. N. O.). The results for the third subject were essentially the same as these. In this graph, the abscissas are the angular size of the test target, given in both the angular separation of the squares of the checkerboard pattern in minutes of arc and also the equivalent Snellen notation. The ordinates give the depth of focus in diopters. The values plotted are those for the 50% level and those estimated for the 99% level of probable visual resolution of the target. Each point plotted here represents the average of three complete sets of data obtained on different days. Individual points again represent the mean result of the analysis of at least 600 observations.

Inspection of this typical graph shows a relatively rapid change in depth of focus at the small target sizes. Indeed, below the 20/25 target size, the depth of focus estimated at the 99% level for this observer rapidly fell to zero. With larger target sizes, however, the curves approach a straight line. This straight-line tendency was found to be true for all observers for the target range above the 20/25 target size and indicates that the depth of focus increases proportionally to the increase in target size in this range. On the basis of our data, this depth-of-focus increase is about 0.3 to 0.4 D. per five-unit step of Snellen notation, such as from 20/25 to 20/30 and 20/30 to 20/35.

Depth of Focus and Size of Pupil.—As is well known, the depth of focus increases as the pupil decreases in size. The quantitative relationship between the depth of focus based on loss of visual acuity and the size of pupil is, however, by no means clear. A number of factors associated with pupil size, such as spherical aberration, diffraction effects, and the Stiles-Crawford phenomenon, will play a role.

In this basic study we wished to avoid the use of artificial pupils for several reasons:

They greatly restrict the field of view, and during the experiments they introduce a constant problem of centering; furthermore, the more normal dioptric imagery on the retina is changed, and, of course, artificial pupils of greater than the normal prevailing pupil size cannot be used without premydriasis anyway. Consequently, in these experiments the pupil size of the observing right eye was altered with appropriate drugs. Phenylephrine (Neosynephrine) (10%), hydroxamphetamine (Paredrine) (1%), and pilocarpine (0.5% and 1%) were employed.

The use of drugs, to be sure, introduced other problems, the greatest being the maintenance of a constant miotic or mydriatic effect. Prior to actual measurements on depth of focus, the course of pupillary response of each subject to each drug was determined by photographing the entrance pupil under the experimental conditions at frequent intervals of time after drug instillation. From a graph showing the variation in size of pupil with time, the optimal period for obtaining depth-of-focus measurements could be determined, as well as the time when additional drugs should be instilled in order to maintain as constant a pupil size as possible.

An additional problem, which was not entirely anticipated in degree, arose as a result of the effect of pilocarpine on accommodation. In the youngest subject the instillation of two drops of 0.5% pilocarpine rapidly produced a myopia to the degree of approximately 1.5 D. This effect so rapidly progressed, then dissipated, that the changing focus prevented accurate accumulation of data by our technique. On only the partially presbyopic subject were both the 0.5% and 1% pilocarpine employed satisfactorily. For the third subject, data were taken only with the 0.5% strength of this drug. During the period when data were actually taken, photographs of the pupils were again repeated at spaced intervals.

The results of measurements on the depth of focus of the eye for entrance pupils of different sizes, as produced by the drugs, are summarized for one subject in Table 3.

The results for another observer for 13 separate depth-of-focus determinations, at the 50% level of probability of visual resolution, are shown in Figure 7. The ordinates again indicate the depth of focus in diopters, and the abscissas indicate the diameter of the entrance pupil in millimeters. All measurements were made on the observer on different days and with the drugs indicated. This graph shows the spread of data about a line assumed to describe the mean course of the change of depth of focus with change in pupil size. The plot shows the anticipated inverse relationship: the larger the pupil, the smaller the depth of focus.

The average results for the three subjects are shown graphically in Figure 8. The individual points for each subject represent the mean depth of focus at the 50% level for the mean entrance-pupil size for all sets of measurements obtained with use of the

TABLE 3.—*Summary of Data for One Subject (J. T. S.) for Change in Pupil Size Induced by Drug* *

	Drug Used			
	Pilocarpine, 0.5%	None	Phenylephrine (Neosynephrine), 10%	Hydroxamphetamine (Paredrine), 1%
Average size of entrance pupil, mm.	2.50	3.90	5.90	6.20
Depth of focus, 50% level, D.	1.33	1.04	0.88	0.82
Depth of focus, estimated at 99% level, D.	0.78	0.75	0.48	0.35
σ for proximal distribution, D.	0.09	0.06	0.09	0.13
σ for distal distribution, D.	0.15	0.06	0.09	0.07
Displacement of midpoint, 50% level, D.	−0.82	−0.26	−0.23	−0.24
Displacement of midpoint, 99% level, D.	−0.62	−0.27	−0.23	−0.17

* Target size, 20/25; exposure time, 1/5 second.

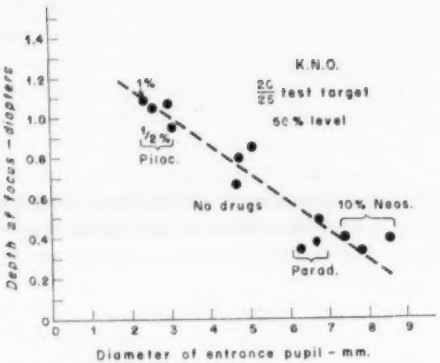

Fig. 7.—The results of separate sets of measurements of the depth of focus of the eye for one subject, for entrance pupils of various sizes, as produced by the drugs.

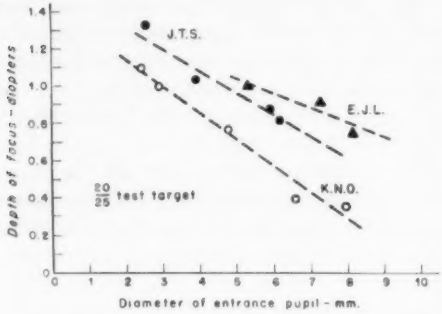

Fig. 8.—The results for three subjects showing the change in the depth of focus of the eye at the 50% level of probable visual resolution, with change in entrance-pupil size induced by drugs. Each point is the mean of three separate sets of measurements.

same drug. Although it may be theoretically incorrect to do so, straight lines have been fitted to these data points.§ However, if the discussion is restricted to a range of pupil diameters from 2.5 to 8 mm., this representation may be permissible practically. Within this range there is a proportional increase in depth of focus with decrease in size of pupil. The rate of change of depth of focus with a given change in diameter of pupil would be expressed by the slopes of these lines. Only three points were available to determine the curve of Subject E. J. L., and therefore the resulting slope should probably be accepted with caution. However, the tabulated slopes of the lines for the three subjects are given in Table 4. Included are the slopes for the lines obtained from the estimated depth of focus at the 99% level as well as those from the depth of focus at the 50% level of probable visual resolution.

Over the range of pupil size tested, then, the depth of focus was found to decrease approximately one-eighth of a diopter for each millimeter of increase in pupil diameter.

§ On the basis of simple geometry and a constant limiting blur circle on the retina, there should be a mathematical reciprocal relationship between depth of focus and pupil size. Thus, as the pupil size becomes very small, about the size of a pinhole, the depth of focus should be very large. Theoretically, therefore, one would expect a hyperbolic rather than a straight-line relationship.

TABLE 4.—*Diopters Change of Depth of Focus Per Millimeter of Increase in Diameter of Pupil*

Subject	Pupil Range	50% Level	99% Level
K. N. O.	2.4 to 8.0	−0.15	−0.15
J. T. S.	2.5 to 6.2	−0.11	−0.13
E. J. L.	5.3 to 8.3	−0.08	−0.12
Average		−0.11	−0.13

Comment

A consideration of depth of focus must be taken into account when attempts are made to determine the range of clear vision with the use of various visual aids, particularly in the use of multifocal lenses by presbyopes.[11] The depth of focus, of course, bears directly on the range of effective vision among those persons subject to so-called night myopia or empty-field myopia, as they may involuntarily accommodate when subjected to these featureless environments. In order to estimate the range of clear visual resolution for these persons (for example, the high-altitude flier or one experiencing "white-out" in the arctic), recourse to empirical data on the depth of focus is necessary.

Although in the literature depth of focus has not been stressed as a factor in the action of miotics, such as di-isopropyl fluorophosphate (DFP), in the treatment of convergence excess, it is not unlikely that the greatly increased depth of focus result-

ing from such extreme miosis would play a major role in the apparently decreased demand for accommodation.

The results reported herein with the checkerboard test target used under controlled conditions must be regarded as fundamental. However, when applied directly to the use of the Snellen letter chart clinically, some variance might exist because of recognition factors and the like that play a role in the legibility of letters, because the chart can be observed for longer periods than ⅕ second as used here,‖ and because there would be more or less exact foveal fixation.[12] Further, we are not certain that the task of discriminating the checkerboard pattern is an exact equivalent to the task of discriminating the "average" Snellen letter of equal subtense.[13] One might expect the acuities as expressed in this paper to be on the conservative side when compared to their clinical counterpart.

Bearing these points in mind, we may take the depth-of-focus values as determined here as truly "working" figures for use in clinical situations.

For example, consider the determination of refractive correction for distant vision. Suppose we take the depth of focus for the letter size Snellen 20/25 to be 0.76 D. at the 99% level of discrimination and 1.04 D. at the 50% level, as actually found for one subject. Then, if this subject were being "fogged" at postcycloplegic refraction, he could read approximately half of the letters on the 20/25 line when myopic 0.5 D., and he could read all the letters on this line while still myopic nearly 3/8 diopter. This conclusion once more affirms the necessity of reducing the amount of plus power (fog) until no smaller letters are discriminated. Since some persons have a significantly large depth of focus for size 20/20 letters, their "best" refractive correction must be determined with the use of letters smaller than those of the 20/20 line.

The data presented in this paper also bear on the problem of the relationship between visual acuity (resolving power) and refractive error. For example, can the myopic error (spherical) be estimated when a patient can read only 20/25? Actually, the data shown graphically in Figure 6 provide this information if we divide the values for depth of focus by two. This is to say, the maximal allowable spherical error associated with a certain visual acuity is approximately equivalent to half the depth of focus for that acuity.

In a previous study [11] existing clinical data for the visual acuity found with corresponding uncorrected spherical refractive errors were correlated. This study indicated that the logarithm of the visual acuity was directly proportional to the uncorrected refractive error. When our data are plotted, with half the depth of focus as estimated at the 99% level of probable visual resolution as the abscissa and the logarithm of the resolving power or of the visual angle as the ordinates, we obtain the graph shown

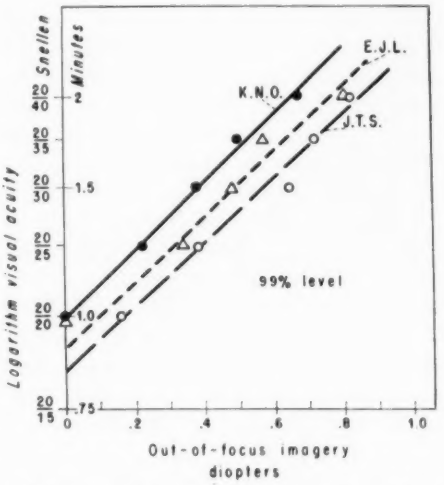

Fig. 9.—Relationship between half of the estimated depth of focus at the 99% level of probable resolution (analogous to the degree of uncorrected myopia) and the logarithm of the visual angle subtended by the details of the test target to be visually resolved.

‖ Subsequent experiments to be reported later show that with binocular observation the depth of focus increases about 25%, from ⅕ to ½ second, and that there is little additional increase for longer exposures.

in Figure 9. Straight lines have been drawn through the points by inspection. The fact that straight lines seem to describe the data adequately again indicates a proportional relationship between the logarithm of the visual acuity and the uncorrected spherical refractive error. The existence of this proportionality supports the design of visual acuity test charts of the Snellen type, for which the size of the letters on each line bears a constant ratio to the size of the letters on the adjacent line below.

Summary

The criterion of the loss of resolving power (visual acuity) with increase in out-of-focus imagery was used in making measurements on the depth of focus of the human eye. Psychophysical methods with the checkerboard visual acuity test chart were utilized. All test conditions were held constant, binocular vision was maintained, and time of exposure of the test target was 1/5 second. For three subjects the mean total depth of focus, obtained by means of a test target with resolvable details of angular size equivalent to 20/25 Snellen notation, was found to be 0.94 D. at the 50% level and estimated to be 0.63 D. at the 99% level of probable visual resolution of the target details. The effect of changing two experimental conditions was determined: (1) the change in depth of focus with increase in the angular size of the test target and (2) the change in depth of focus with change in pupil size. It was found that for each five-unit step of increase in target size, as from 20/25 to 20/30 (through the range 20/25 to 20/40), the depth of focus increased by 0.3 to 0.4 D. It was found also that over the range of change in size of pupil from 2.5 to 8.0 mm., the total depth of focus decreased about 1/8 diopter per millimeter of increase in size of the pupil. These results are reviewed briefly with respect to certain practical applications.

Mayo Clinic.

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Evaluation of a Screening Procedure in the Detection of Eye Disease

VERA CASSIDY, R.N., and WILLIAM H. HAVENER, M.D., Columbus, Ohio

Although the incidence of blindness in the United States is the lowest of any major nation (54 per 100,000), preventable blindness still occurs far too frequently. Despite the efforts of the ophthalmologists, the general practitioner, and the public health workers, there are now 17,000 legally blind persons in Ohio—enough to populate a small city. Improvement of these statistics of tragedy would be possible by application of existing knowledge through earlier detection and treatment of serious eye diseases.

A proven and fruitful method for early detection of serious disease is the widespread use of well-chosen screening procedures. The objective of a screening procedure is not to diagnose disease but to detect persons who are likely to have disease, in order to permit referral for definitive study and care. The ideal screening method should not fail too many normal persons (false-positive result) and, more important, should not overlook any case of disease (false-negative). A practical screening method cannot be time-consuming and should not be too complicated to administer.

Early detection of glaucoma is a particularly profitable objective of screening tests because of the high incidence of glaucoma (2% of the population over 40 years of age; 10% of all blindness) and because of the greatly improved prognosis of glaucoma brought under treatment in its early stages. The characteristics of glaucoma which can be detected by screening include increased intraocular pressure, field loss, and visual acuity loss. We are completely convinced that routine tonometry is far superior to any other screening test for glaucoma. Unfortunately, among both physicians and laymen considerable resistance is encountered to the idea of touching the cornea with an instrument. Another disadvantage of routine tonometry is that it is such a specific test. It will not detect any disease except glaucoma. Perimetric methods of screening have the advantage of detecting any of the great variety of eye diseases causing field defects (including opacities of the media). They do not require any disturbing contact with the eye itself. However, glaucoma detectable by perimetric methods is necessarily a stage of the disease which has advanced to permanent loss of part of the optic nerve. Visual acuity examination is almost useless in detection of glaucoma at an optimal stage. An exception to this is the patient with asymmetric glaucoma, far advanced in one eye only. On the other hand, visual acuity is a simple accurate determination of great value and should be required in every complete physical examination.

This paper will present the results of the screening of 1,536 persons with use of the Harrington-Flock Multiple Pattern Field Screener. The great majority of these were patients from the Ohio State University Ophthalmology Clinic. A small number of private patients and normal medical personnel were included. A great variety of eye and general disease was present in this group of patients. Children as young as 5 years and adults to the age of 88 years were included. Clinic patients were examined consecutively without selection except that the examiner (Mrs. Cassidy) could not be present every day and missed all patients on these days. In addition,

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very ill and disabled patients could not be positioned before the screener.

Harrington Screener

The Harrington Screener is a multiple-pattern method of visual-field examination which is based on the principle of tachystoscopic or flash presentation of simple patterns of dots and crosses to the fixing eye. The dots and crosses serve as visual stimuli in selected parts of the visual field. The objects on the patterns are printed with fluorescent sulfide ink. The metal box in which the pattern book is fastened through its ring binding measures 18 in. square, 6 in. deep in front, and 2 in. deep posteriorly. The cover is hinged, and when open it supports the pattern cards. The black light tube with its transformer and connections is contained in a compartment below the chin rest so that ultraviolet radiation is directed against the opened box lid and illuminates the test objects.

The light is controlled by three switches: 1. A lever-type switch turns on the line current. 2. A black push-button switch turns the light on and off by manual control. 3. A red push-button switch flashes the light on for a measured quarter of a second.

An occluder, fastened to a bar on the chin rest, can be moved from side to side to cover either eye. This occluder is not very effective, since it cannot be raised or lowered to accommodate various size patients. Correction of this defect could easily be made with a larger occluder or an adjustable height mechanism. We routinely used an eye patch (protecting against spread of infection by placing a tissue between eye and patch) rather than the occluder furnished with the instrument.

It is absolutely necessary that the instrument be firmly positioned on a table which can readily be raised or lowered to the proper position before the patient.

Technique

The examiner should face the patient or stand at the side so that the patient's position and fixation can be readily observed. The patient is instructed to place his chin midway on the chin rest. He is then directed to fix his uncovered eye on the black dot located in the center of the white pattern card. He is told that a brief flash of bluish light will illuminate a design of dots and crosses on the card and that he should state the *number* of dots or crosses which he sees. The examiner then begins the test. Correct responses are *not* recorded, but objects missed are marked with a red pencil on the composite pattern chart. It is important that the Harrington Screener be located in an area which is fairly free of noise and distractions.

Observations

Many patients, both old and young, become confused by the request for a *number* response, rather than for a description of what was seen. Further explanation usually resulted in satisfactory performance. If this did not help, responses such as "one in each corner," "one dot on the left, one cross on the right," or "three lights" were accepted. Actual time for completing the test was prolonged two to three minutes by this type response. The usual screening time was less than five minutes.

Older patients responded more slowly and made up the majority of false-negatives and false-positive groups. This group complained that the light flashed too rapidly and needed encouragement to complete the test.

The children tested responded rapidly without requiring additional instruction. Children as young as 5 years were successfully examined. We believe the Harrington Screener can be used almost as soon as a child has learned to count.

The degree of attention with which the patient regarded the test was important. Those who were interested and alert had no difficulty. Others who were tired, ill, or lacked interest or intelligence called numbers at random.

Card No. 4, consisting of two dots above and two below the fixation point, usually received a response of "six" from those

who either didn't understand instructions or didn't take time to think about what they saw. This served as an indicator for further instructions which usually brought successful results.

Many patients with vision as poor as 5/200 responded rapidly to the test. Generally visual acuity did not seem to influence results, unless the decrease was due to disease, such as not operated-on cataracts, rather than to refractive errors. Decrease in visual acuity may have accounted for the not infrequent complaint that the fixation dot was too small.

Results

A total of 1,536 persons were tested by the Harrington Screener. Of this number, 1,260 (82%) did not have diseases causing field defects and were classified as "normal." There were 39 (2.5%) "false positives." "False negatives" totaled 26 (1.7% of the entire group). Recalculated in terms of the number of abnormalities which should have been detected by perimetric testing, 26 of 228 (11.5%) were false negatives by the screening method. Two hundred two patients (13%) showed abnormalities by both routine perimetry and Harrington screening. It was noteworthy how closely the defects mapped by the two methods corresponded. Nine examinations were so equivocal as to prevent classification in the above categories.

False Positives

The false-positive group consisted of 39 patients (2.5%) found to have abnormal screening results but who could not be proven to have perimetric abnormalities or diseases which are expected to cause field defects. It is evident that most of the patients classified in this group did have some type of eye disease which warranted ophthalmologic care (refractive error, etc.). Most false-positive patients were over 50 years of age.

Diagnoses falling in this group were as follows:

1. Superficial infections, such as keratoconjunctivitis (six patients). Apparently increased tearing, discharge, and irritation cause irregular defects in the screener results (Fig. 1). Repeat screening after recovery gave normal findings.

2. Aphakia (10 patients). It can easily be demonstrated that the aphakic eye is far more sensitive to ultraviolet light than is the normal eye. In aphakia the Harrington-Screener flash is seen to illuminate the entire test card so brightly that the test figures are not conspicuous enough to recognize (Fig. 2).

3. Cataracts not operated on (nine patients). We were at first disturbed to find in these patients central defects similar to those of senile macular degeneration. This response is due to the blurred image of the four small central dots, which cannot be distinguished separately (Fig. 3).

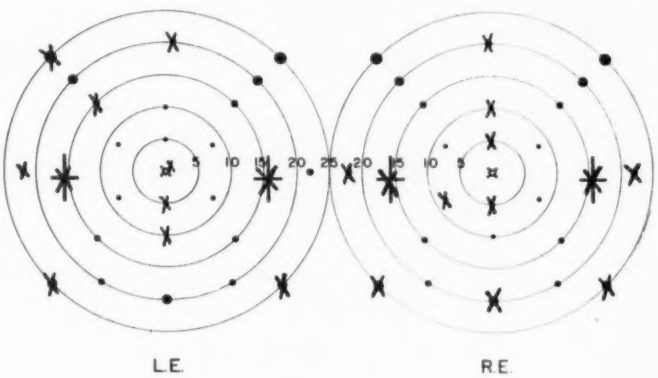


Fig. 1.—False positive O. U. Superficial infections, such as Keratoconjunctivitis, cause irregular screener results. Increased tearing, discharge, and irritation seemed to be responsible for this response.

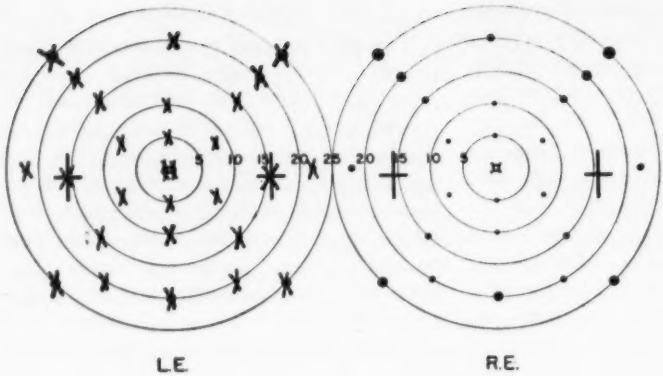
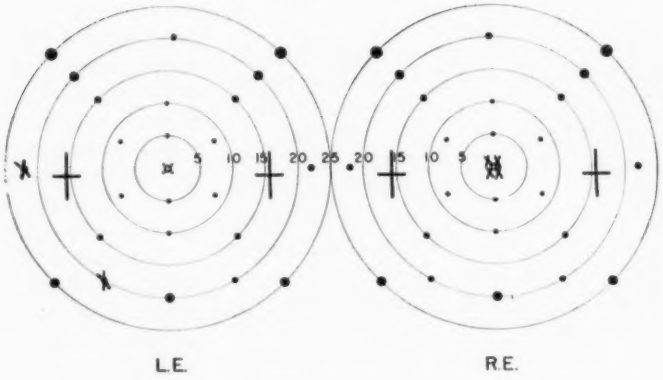


Fig. 2.—False positive O. S. Aphakic eyes are more sensitive to ultraviolet light than normal eyes, therefore the Harrington Screener flash is seen to illuminate the entire card so brightly that the test objects cannot be distinguished.

Fig. 3.—False positive O. D. Cataracts not operated on simulate a central defect due to the blurred image of the four central dots.



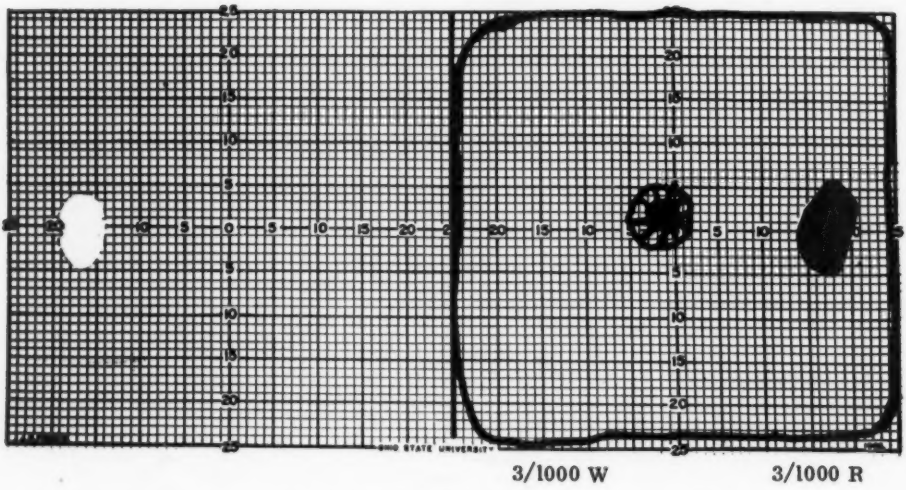


Fig. 4.—False negative O. D. Chorioretinitis. Lesions peripheral to Screener pattern or located between the patterns cannot be detected.

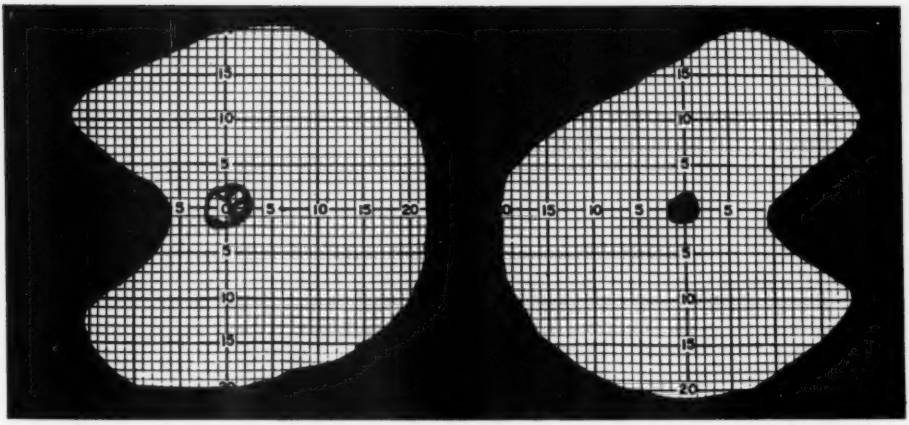


Fig. 5.—False negative. Early senile macular degeneration. These central defects were too small to be elicited by the screener.

Fig. 6.—False negative O. U. Hysteria. Very often a patient with diagnostically constricted fields would show no screener defect.

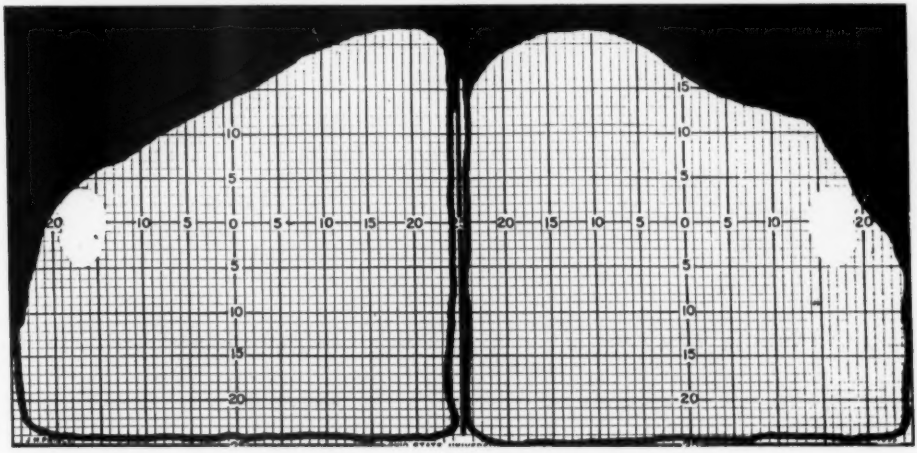


Fig. 7.—False negative O. U. Neurologic disease (acromegaly). Small early defects, such as enlargement of the blind spots or sector defects, were not always detected by the screener.

4. Miscellaneous (14 patients). No explanation could be found for the irregular fairly consistent defects in this group.

An inexperienced operator tends to diagnose more false positives. Many false positives can be proven such by immediately repeating the test. Unnecessary referrals may be avoided if the second examination is normal. Close observation of the patient often indicates whether the patient is fixing constantly and is giving his complete attention to the examination. Proper position is

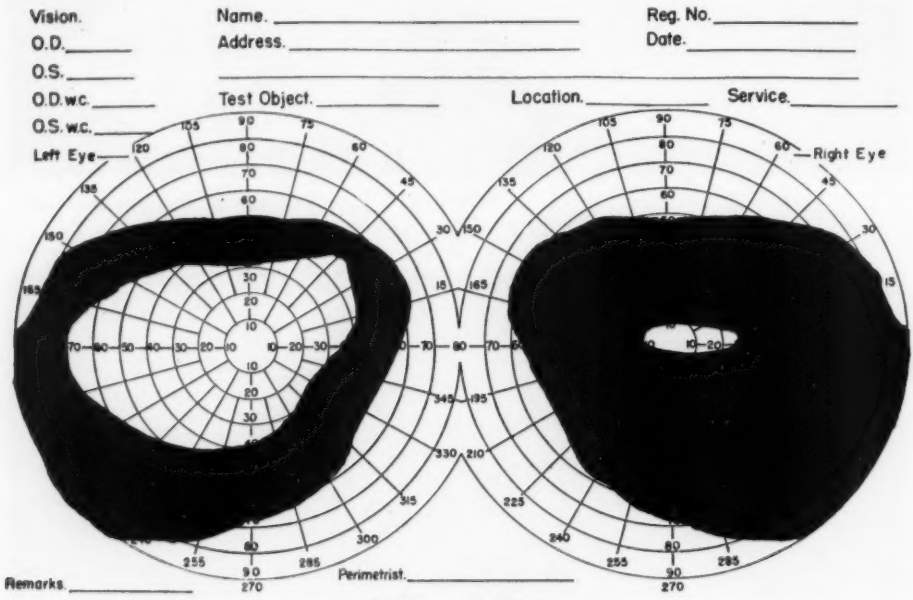
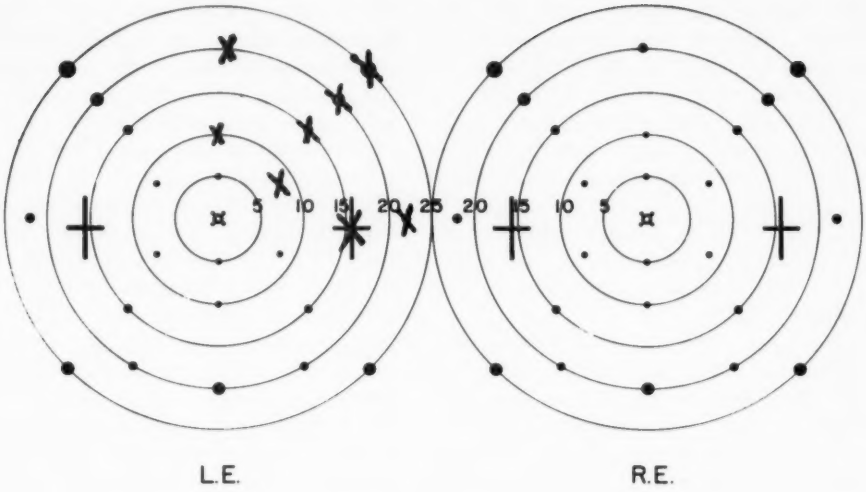


Fig. 8.—False negative. Glaucoma. The screener often failed to detect Seidel scotomata, baring of blind spots, and peripheral constriction.



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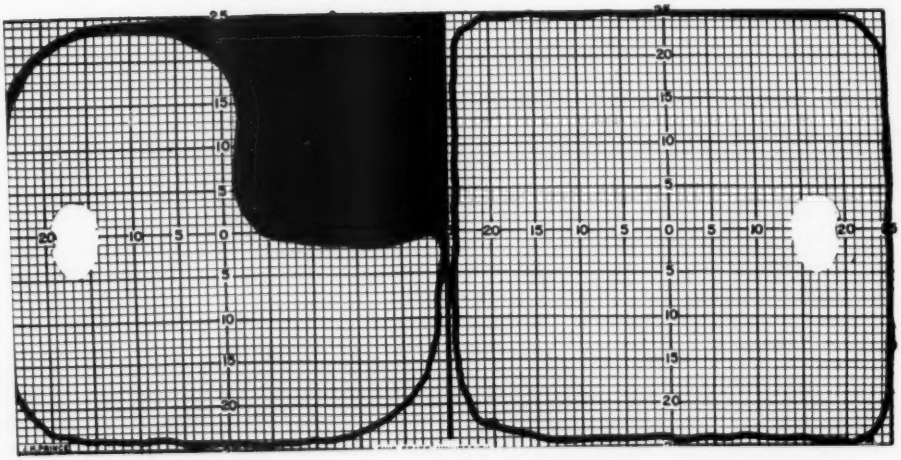

Fig. 9.—Abnormal by both methods. Chronic simple glaucoma representing a sector defect which was shown by both methods.

also a factor to be considered. If the box is too high the patient tends to miss pattern objects below the chin level. The opposite is true if the box is too low.

If the patient seems slow or confused, it may be desirable to repeat the possibly false-positive test with use of the manual switch and illumination of the test patterns for a longer time. With longer illumination it is absolutely essential that central fixation be maintained. If the same defect is plotted with this method, a field loss certainly is present.

False Negatives

The false-negative group contained 26 patients (1.7% of the total) whose screener examinations were entirely normal despite

the presence of perimetrically detectable disease. Most of these patients were over 50 years of age. The following types of field defects were missed.

1. Chorioretinitis (eight patients). Lesions peripheral to the screener pattern or located between the patterns could not be detected (Fig. 4).

2. Early senile macular degeneration (three patients). While the central scotoma was small, it was not detected by the screener (Fig. 5).

3. Hysteria (three patients). These were unpredictable, but remarkably often a patient with diagnostically constricted fields would show no screening defect (Fig. 6).

4. Neurologic disease (four patients). Small early defects, such as enlargement of the blind spots or sector depression, were not always detected by the screener (Fig. 7).

5. Early glaucoma (eight patients). The screener often failed to detect Seidel scotomata, baring of the blind spot, and peripheral constriction (Fig. 8).

In order to state honestly what proportion of patients are false negatives, calculations should be based upon the number of patients with known perimetric defects rather than the total number of patients. There were 26 false negatives in 228 patients with field abnormalities. This means the screener missed 11.5% of the defects it could have been expected to disclose.

These missed defects were all quite small; nevertheless, it must be emphasized that use of the screener is *not* an adequate substitute for accurate perimetry in evaluation of the early cases of field loss. Screening will miss a very large proportion of these smaller lesions.

Glaucoma patients were not failed by the screener until definite field loss was evident. Thus as would be predicted, the screener is of no value in detecting early glaucoma and missed 8 out of our 37 glaucoma patients.

Abnormalities by Both Screening and Perimetry

Two hundred two cases were included in this group. Whenever pronounced field defects were present, the screener was a remarkably effective instrument. The separation between screener patterns is so great that screening is not delicate enough to use in doing serial fields to follow a patient. The following diseases caused demonstrable defects by both methods: (1) cataracts (39 patients); (2) senile macular degeneration (33 patients); (3) glaucoma (29 patients, Fig. 9); (4) chorioretinitis (26 patients); (5) hypertensive diabetic retinopathy with hemorrhage (11 patients); (6) optic atrophy (9 patients); (7) neurologic defects (9 patients, Fig. 10); (8) retinitis pigmentosa (7 patients); (9) retinal detachment (7 patients); (10) optic neuritis (6 patients); (11) hysteria (8 patients); (12) pituitary tumor (3 patients), and (13) miscellaneous (15 patients).

Visual Acuity

The remarkable value of reduced visual acuity as a screening test is often overlooked. Let us arbitrarily classify corrected vision of 20/40 or less in the worse of the two eyes as failing the visual acuity test. This acuity is selected because it is bad enough to permit little confusion with 20/20 vision. Vision reduced to 20/40 or less was present in 85% of the patients with perimetric defects, 52% of the false-negative screener patients, and 24% of the total 1,536 patients.

The figures speak for themselves. Visual acuity testing is obviously a most valuable screening method. Since it measures the functional ability of the eye, it will be altered by and will detect a wide variety of diseases.

Summary

The Harrington-Flock Multiple Pattern Screener was used to test 1,536 persons in the eye clinic. Routine perimetric methods were used to confirm findings.

Two hundred two patients (13%) showed abnormalities by both screener and perimeter.

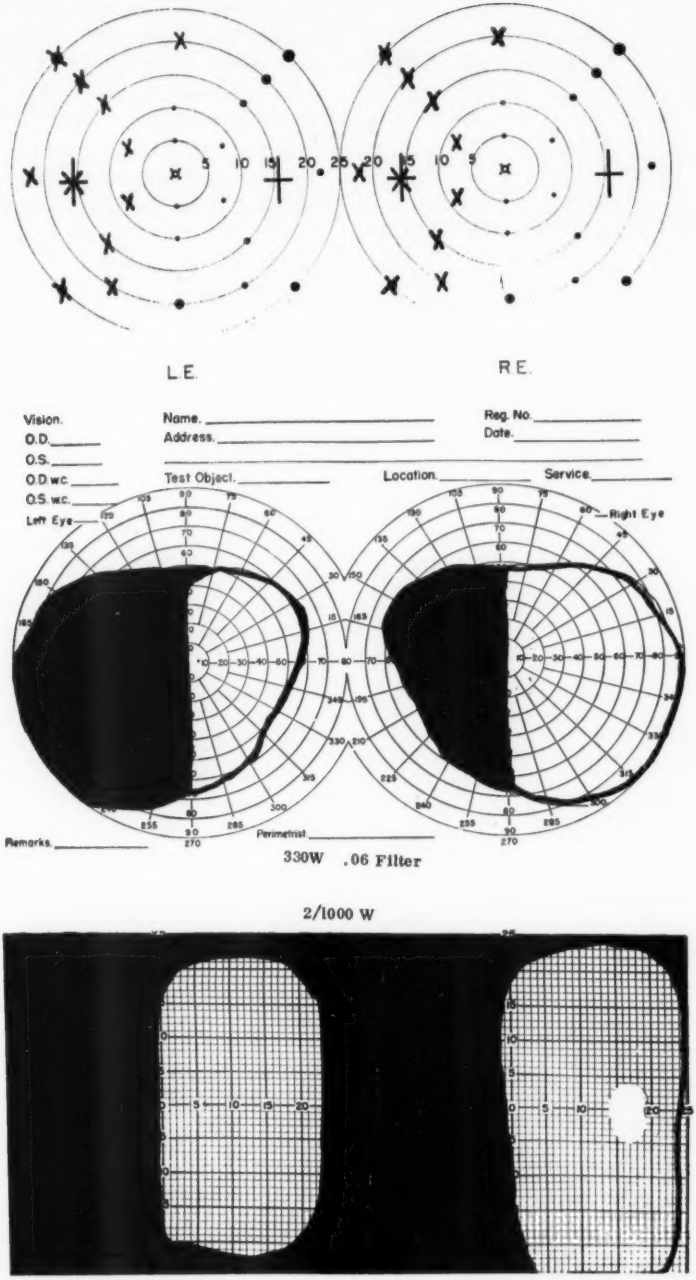

Fig. 10.—Congruous left hemianopia with macular splitting, a neurological defect which was shown by both methods.

Thirty-nine (2.5%) false-positive tests were found.

Twenty-six (1.7%) false-negative tests were recorded. These represented 11.5% of the 228 patients who had perimetrically detectable defects. Since the screening test often misses early field defects, it cannot be substituted for standard perimetry in the study of patients strongly suspected of having perimetrically demonstrable disease.

Eighty-five per cent of the patients with perimetrically demonstrable defects had visual acuity uncorrectibly reduced to 20/40 or less in at least one eye. *Simple measurement of visual acuity is a most valuable screening method.*

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Department of Ophthalmology, University Hospital (10).

Ocular Findings in Brain Tumors in Children

ULYSSES M. CARBAJAL, M.D., Los Angeles

The purpose of this paper is to present the commonest ocular findings in children with brain tumor and to elucidate the role of the ophthalmologist, in conjunction with the pediatrician, the radiologist, and the neurological specialist, in the diagnosis.

Case Material

The hospital records of 211 patients admitted to Los Angeles Childrens Hospital during the last 20 years with the diagnosis of brain tumor have been reviewed by me, with emphasis on the ocular findings. Although all of these patients were admitted to the neurosurgical service, an ophthalmological consultation was requested for many of them. A number of these patients were personally seen by me in the eye clinic and/or on the wards. In 172 patients, the diagnosis of brain tumor was histologically confirmed at operation and/or autopsy. In the majority of the remaining 39 patients, intracranial exploration was not done. In a few subjected to craniotomy, either the specimen was not adequate or the examination was not satisfactory enough for classification.

Results

The most important ocular finding in this study was papilledema, which was found in 127 (74%) of the 172 patients whose brain tumors were verified by microscopic examination. Table 1 gives a classification of papilledema as to unilaterality and degree. Except in a few patients, the degree of papilledema in bilateral cases was about the same in either eye.

TABLE 1.—*Classification of Papilledema (127 Patients)**

	No.
A. Unilateral or Bilateral	
Unilateral	10 (7%)
Bilateral	117 (93%)
B. Degree of Papilledema	
Early	41
Moderate	45
Marked	36
Long-standing	5

* As observed soon after admission.

In this paper, the term "papilledema" means passive noninflammatory edema of the discs,[1] regardless of the intracranial pressure. It varied in its ophthalmoscopic appearance according to its stage and the rapidity of its development. In patients with early papilledema, two or more of the following were noted: hyperemia of the disc, blurring of the disc margins (upper and lower or nasal side first), blurring of the details of the physiologic cup, overfilling or slight engorgement of the veins.* In those where papilledema was moderate, the above findings were present and the disc was elevated by not more than 3 D. Hemorrhages were noted around the disc in six patients. In those with marked papilledema, the disc was elevated by 4 to as much as 8 D. Moreover, the margins of the disc were definitely blurred, the vessels were seen to climb to attain the disc, the veins had become further engorged, and hemorrhages had appeared as linear streaks on the disc or around it. In two patients, a fan-shaped arrangement of exudate was seen extending from the macula towards the disc. The five cases

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From the Eye Department, Los Angeles Childrens Hospital, and University of Southern California School of Medicine.

* Digital pressure on the eyeball to elicit venous pulsation was rarely done in this series. Walsh[1] considers lack of venous pulsation on the disc strongly in favor of early papilledema.

classified as long-standing papilledema (or advanced papilledema) showed irregular margins, sometimes with pigment deposits, and the disc had become grayish because of glial proliferation. The elevation of the disc had diminished, the arteries had narrowed, and the turgidity of the veins had slackened somewhat. Extreme optic pallor and definite excavation was observed in one patient.

The brain tumors in this series are grouped after Cushing's [2] classification, and the incidence of papilledema in each group is tabulated in Table 2. Gliomas were associated with papilledema in 77%, in contrast to craniopharyngioma, which was accompanied by papilledema in only 46%. It is easy to understand why tumors of the choroid plexus were associated with papilledema in 75% of the cases.

It is demonstrated in Table 3 that supratentorial tumors in children may give rise to papilledema as frequently as those located subtentorially. This finding appears contradictory to the commonly accepted fact that the incidence of papilledema should be higher in patients with subtentorial tumors than in those with supratentorial. This is based on the fact that the former location is conducive to obstruction in the region of the aqueduct of Sylvius, which gives rise to internal hydrocephalus and, of course, papilledema. Another salient finding depicted in Table 3 is the low incidence of papilledema (31%) in pontine and cerebellopontine tumors.

The visual fields were plotted † in 52 patients, half of which showed some abnormality (Table 4). In the few where the fields were done by me it was extremely difficult to make the patients fixate the center of the screen. This was due not only to age but also to the fact that the children were often suffering from headache and/or vomiting and their minds were not clear.

Nystagmus (Table 5) was noted in 59 patients and was chiefly in the horizontal

TABLE 2.—*Relationship of Tumor Type and Papilledema*

Tumor Type	Papilledema		Total
	Present	Absent	
Gliomas *	105	31	136
Pituitary adenomas			0
Meningiomas	1	3	4
Acoustic tumors	0	1	1
Congenital tumors			
Craniopharyngioma	7	8	15
Metastatic & invasive tumors †	4	0	4
Granulomatous tumors			
Tuberculoma	1	0	1
Blood vessel tumors			
Hemangioendothelioma	2	0	2
Primary sarcomas			0
Tumors of the choroid plexus			
Papillary adenocarcinoma	3	1	4
Cysts	2	0	2
Cranial tumors involving brain			
Chondrosarcoma	1	0	1
Others	1	1	2
Mixed-cell tumor 1			
Neurofibroma 1			
Total	127	45	

* Astrocytoma, 51; astroblastoma, 2; glioblastoma, 13; medulloblastoma, 28; spongioblastoma, 9; ependymoma, 13; ependymoblastoma, 1; pinealoma, 2; ganglioneuroblastoma, 1; unclassified gliomas, 16.

† To be comparable with previous classifications, the 9 cases of retinoblastoma metastasizing to the brain have not been included in this series.

TABLE 3.—*Relationship Between Location of Tumor and Papilledema*

Location	Papilledema		Total
	Present	Absent	
Supratentorial			
Cerebrum	21	6	27
Basal ganglia	3	1	4
Suprasellar area	7	8	15
Pituitary			0
Chiasm	1	0	1
Pineal gland	2	0	2
Blood vessels	2	0	2
Lateral ventricle	6	1	7
Third ventricle	8	1	9
	50 (74%)	17 (26%)	67
Subtentorial			
Cerebellum	40	9	49
Pons	5	9	14
Cerebellopontine angle	1	4	5
Fourth ventricle	19	4	23
Medulla	2	1	3
	67 (71%)	27 (29%)	94
Others			
Cranium	3	0	
Location not specified	7	1	8
	10 (90%)	1 (10%)	11
Totals	127	45	172

† Large targets or even hand movements had to be used to catch the attention of many of the patients.

TABLE 4.—*Field Changes in Fifty-Two Patients*

	No.	
Abnormal fields		26
Homonymous hemianopsia	9	
Contraction of fields	8	
Bitemporal hemianopsia	5	
Others	4	
Normal fields (gross)		26

TABLE 5.—*Type of Nystagmus in Fifty-Eight Patients*

	No.	
Jerky		43
Just horizontal	30	
Vertical & horizontal	5	
All directions	8	
Pendular (nystagmoid, searching, wandering, etc.)		6
Not specified		9

plane and of the jerky type. It was observed mostly in patients with cerebellar lesions and rarely in patients with midline tumors. The character of the nystagmus differed according to the direction of gaze, being slower and coarser when the eyes were deviated away from the side of the tumor.

As will be noted in Table 6, ocular palsies were observed in 49 children. Twenty-five patients definitely had sixth nerve palsy, 13 might have had abducens palsy, but all that was recorded was a unilateral esotropia. The third nerve was possibly involved in five. As will be pointed out later, ptosis was seen in five patients. It is highly probable that a few of the children with unilateral esotropia may have had a comitant strabismus; that is, the ocular palsy may not have been related to the tumor.

The most consistent pupillary sign in brain tumor was a sluggish reaction of the pupil to light and accommodation. Table 7 shows the other pupillary signs.

TABLE 6.—*Ocular Motor Palsies in Forty-Nine Patients*

	No.	
Esotropia		38
Definite sixth nerve palsy	25	
Unilateral	17	
Bilateral	7	
Unknown	1	
Questionable sixth nerve palsy	13	
Exotropia (possible third nerve palsy)		5
History of double vision, but normal during examination		4
Gaze palsy		2
Left lateral	1 *	
Upward	1 †	

* This showed at autopsy a large papilloma in the right lateral ventricle.

† Case of pinealoma.

In only 19 patients were visual disturbances mentioned in the history. In these patients, the tumor was most frequently in the occipital lobe or above the sella turcica. Usually one eye was blind for a few weeks before admission to hospital, and it was not until the second eye began to fail that the parents became alarmed. In one case, the patient had been blind for six months prior to admission.

As if by coincidence, 19 patients also showed pallor of the disc, suggestive (not necessarily indicative) of optic atrophy. Two patients had well-defined paper-white discs (primary type of optic atrophy), while the rest had ill-defined borders, characteristic of postpapilledema atrophy.

It is interesting to note that five patients developed unilateral ptosis, which was associated with exotropia in only one case. Table 8 shows the tumor type and location as well as the incidence of papilledema in these patients.

Corneal anesthesia was demonstrated in five patients, in three of whom the tumor was in the cerebellopontine angle.

Four patients developed proptosis, which was bilateral in two. In two children, the

TABLE 7.—*Impairment of Pupillary Reflex in Thirty Patients*

	No.	
Pupils sluggish to light & accommodation		12
Bilateral	3	
Unilateral	2	
Side not mentioned	7	
Anisocorea		8
Dilated pupils		5
Fixed to light		4
Miotic pupils		1

TABLE 8.—*Tumor Type and Incidence of Papilledema in Five Patients with Ptosis*

Case No.	Tumor Type	Tumor Location	Papilledema
1	Glioblastoma	Brain stem	Present
2	Astrocytoma	Optic thalamus, 3d ventricle	Present
3	Acoustic neurinoma	Cerebellopontine angle	Absent
4	Astrocytoma	Pons	Absent
5	Glioma	Cerebellopontine angle	Absent

tumor was invasive; possibly there were metastases to the orbit. Explanation was lacking in the other two.

Lagophthalmus, one of the signs of Bell's palsy, was observed in two patients, both of whom had an ipsilateral glioma in the cerebellopontine angle.

Horner's syndrome was noted in just one patient, who was suffering from lymphosarcoma that had invaded the chest and cranium.

In the lone case showing definite lid lag in the right eye, there was a glioma in the right optic nerve, which extended to the chiasma.

All of the ocular findings in brain tumors in this series are summarized in Table 9.

In this study, a special attempt was made to correlate papilledema with other findings, such as spinal fluid pressure and x-ray findings. Because of the risk of inducing herniation of the cerebellar tonsils through the foramen magnum, spinal tap was done only where the diagnosis was doubtful—as when meningitis or encephalitis was suspected. Out of 39 patients undergoing

TABLE 10.—*Spinal Pressure in Thirty-Nine Patients*

	No.
Low	1
Normal *	8
Slightly increased	5
Increased but less than 300	7
310 to 400	3
410 to over 500	3
Increased but degree not specified	9
Spinal tap done, but pressure not noted	3

* Normal range is 100 to 200 mm. of water.

TABLE 9.—*Summary of Ocular Findings in Brain Tumors in Children*

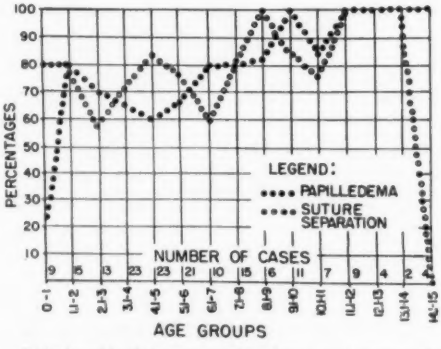
Findings	No. Patients	%
Papilledema	128	74
Abnormal fields *	26	50
Nystagmus	58	33
E. O. M. palsies	49	28
Pupillary changes	30	17
Failing vision	19	11
Optic atrophy	19	11
Others	18	10
Ptosis	5	
Corneal anesthesia	5	
Proptosis	4	
Lagophthalmus	2	
Horner's syndrome	1	
Lid lag	1	

* Fields were done and recorded in only 52 of the 172 patients with verified brain tumors.

spinal tap, 27 showed increased spinal pressure (Table 10). All of these had papilledema of varying degrees.

In 125 patients, x-ray reports were available. Suture separation (cranial) was noted in 87 (94%) out of 92 patients with papilledema; on the other hand, suture widening was noted in 11 (40%) out of 27 patients that did not present papilledema. This indicates either of two things: (*a*) papilledema might not have appeared by the time these patients were seen or (*b*) the widening of the sutures might have prevented the development of significant papilledema.

The Figure bears out the fact that during childhood, papilledema and separation of



Relationship between papilledema and separation of cranial sutures in various age groups.

TABLE 11.—*Degree of Ventricular Enlargement in Sixty-Four Patients*

	No.
All ventricles dilated	14
Two ventricles dilated *	24
One ventricle dilated	14
Borderline	1
Negative	11

* Mostly lateral and third ventricles.

TABLE 12.—*X-Ray Findings in 125 Patients*

	No.
Widening of cranial sutures	87
Enlargement of 1 or more ventricles	64
X-ray changes (calcification, erosion) in or over the sella turcica	22
Increased convolutional markings	8
Calcified tumors	4
Herniation of cerebellar tonsils	2
Enlargement of optic foramen	1
Craniostenosis	1

cranial sutures go hand in hand with no significant disparity, except during the first year of life. It is conceivable that since the cranial sutures are quite stretchable at this stage of development, suture separation can easily take place and even delay the onset of papilledema. At puberty and later, the cranial sutures have begun to be more firm; hence, the incidence of papilledema then outshadows that of suture separation.

In 64 patients whose ventriculograms were reported, only 11 proved negative. Table 11 depicts the degree of ventricular enlargement. The lateral and third ventricles were most commonly involved, the site of obstruction being at the aqueduct of Sylvius. It is noteworthy that in the 12 patients without papilledema where ventriculograms were reported, 10 showed some dilatation of the ventricles. Since papilledema might be considered simply as an indication of increased intracranial pressure, it is highly probable that early papilledema might not have developed. On the contrary, granting that papilledema was truly absent in the aforementioned 10 cases, one would conjecture that enlargement of the ventricle might have been quite gradual or that there might have been some anatomic variation, such as a narrow optic foramen, a small intervaginal space around the optic nerve, or some rigidity of the lamina cribrosa.

Other x-ray findings are summarized in Table 12. Although craniopharyngioma accounted for most of the changes in the area of the sella turcica, there were other types of tumors incriminated, like meningioma and glioma.

A study of Table 13 reveals that sixth nerve palsy was often associated with increased intracranial pressure, as evidenced by presence of papilledema, suture separation, and enlargement of the ventricles. Of these three signs of increased intracranial pressure, papilledema seemed the least reliable, being the last to appear. Again, it is possible that early papilledema might not have been present at the time of the funduscopic examination.

In this series, because of the rather late admission of many of the brain tumor patients to the hospital and the resulting high

TABLE 13.—*Evidence of Increased Intracranial Pressure in Abducens Palsy*

Evidence	Absent	Present	Total	%
Papilledema	18	20	38	52
Suture separation	7	12	19	63
Enlarged ventricle	2	13	15	86
Increased spinal pressure *				

* Not one of the patients with abducens palsy underwent a spinal tap. The diagnosis of brain tumor was very evident in these patients; therefore, spinal tap was deferred. In one patient with sixth nerve palsy, where the tumor was not verified histologically, a shunting operation for extremely increased secretion of cerebrospinal fluid had to be performed.

TABLE 14.—*Follow-Up of Papilledema in Seventeen Patients*

Period of Follow-Up	Pts., No.	Course of Papilledema: Became Normal	Less	Same	Worse	Optic Atrophy
Less than a month	4	0	1	1	1	1
1 mo.	2	2	0	0	0	0
2-4 mo.	6	0	1	1	0	4
5-6 mo.	2	0	0	0	1	1
10 mo.	1	0	0	1	0	0
Over a year	1	0	0	1	0	0
Indefinite	1	Patient had several remissions.				

mortality, only a few patients had a thorough follow-up ‡ of the course of the nerve-head swelling (Table 14). In three patients, the papilledema completely disappeared, despite the fact that in two of these papilledema had been marked. In six patients, the papilledema led to optic nerve atrophy. In four of these, the papilledema was marked; in one, it was moderate; in another, it was early. It is noteworthy that in a 14-year-old boy, the papilledema became worse and nystagmus made its appearance on the day after removal of the brain tumor (astrocytoma). However, both papilledema and nystagmus gradually disappeared, and the patient at the present time is well.

One interesting patient had almost no papilledema on the day of admission, but developed 8 D. of disc elevation overnight. This was due to an intracranial vascular accident. The patient was operated on the following morning, at which time not only was the source of the bleeding found, but also a cerebellar brain tumor was discovered. This proves the point that the development of papilledema can be sudden.

On the other hand, papilledema may make its appearance very insidiously and persist for many months before becoming full-blown, at which time evidence of early atrophy may have made its appearance. There were six cases included in Table 14 that followed this pattern. Of course, the rate of growth of the tumor and its proximity to the ventricular system, especially the aqueduct of Sylvius, greatly influence the course of the nerve head swelling.

It should be mentioned at this point that in this series the more rapid the onset of papilledema, the more hemorrhages were observed around the nerve head and even in the surrounding retina itself. Patients with frank papilledema that persisted two months or more frequently developed optic nerve atrophy. It was also observed in this study that a few cases of the postpapilledema type of optic atrophy characterized by fuzzy disc margins developed later into primary type of nerve atrophy with well-defined borders and even some cupping.

‡ These patients' fundi had been examined and recorded three or more times over a varying period of time.

Comment

The incidence of intracranial tumors without papilledema in this series is 26%, which is higher than those of Critchley's [3] (20%) and of Van Wagenen's [4] (11.7%).

Failure of the discs to undergo choking (papilledema) does not necessarily mean absence of increased intracranial tension. Some of the patients without papilledema in this study showed evidence of increased pressure either at operation or by roentgen-ray examination.

It should be borne in mind that the ocular findings in this series are based on a study of children, where the incidence of cerebellar tumors and craniopharyngioma is much greater than in adults—a finding in harmony with that of Cushing.[2] It would therefore be expected that the incidence of papilledema might be greater among children than among adults. This, however, is counterbalanced by the fact that in children the sutures have a fibrous union which is not yet firm, and therefore papilledema may not be detectable if the increase in intracranial pressure is gradual. Moreover, in children, separation of suture assists in the detection of increased intracranial pressure.

In Newman's [5] series of 23 cases of tumor of the brain in children, 39% had nystagmus and 39% exhibited extraocular muscle palsies. The findings in this series of 172 verified brain tumors (33% and 28%, respectively) are a little lower.

Leinfelder [6] believes that choked disc is not a constant accompaniment of an expanding intracranial mass. More recent observations have shown the incidence of papilledema to be no greater than 50% among patients, both children and adults, with brain tumor. This decrease in frequency is ascribed to the recent progress

made in diagnostic methods,[7] which allow the neurologist, the neurosurgeon, the ophthalmologist, the radiologist, and the pediatrician to make an earlier diagnosis than was formerly possible.

It is worth repeating again what Cushing[2] wrote many years ago: "A median tumor of the cerebellum is so common a lesion in preadolescence that when a child has unexplained vomiting, shows a possible enlargement of its head and gives a story of periodical unsteadiness, it is well to be on guard and to have a look at the eyegrounds every week or two." May I add here that a careful systematic note should be written in the chart concerning the eyegrounds and that one should refrain from writing simply negative fundi, or no papilledema, and so forth. One should take note of the following points: (1) color of the disc; (2) blurring of the margins; (3) blurring of the details of the physiologic cup; (4) engorgement of the veins; (5) hemorrhages and exudates at or around the disc; (6) elevation or protrusion of the disc; (7) absence of venous pulsation. In older children the blind spots should be mapped out accurately.[8]

In borderline cases, one should take advantage of such instruments as the binocular ophthalmoscope, Scheppen's ophthalmoscope, the ophthalmodynamometer, and the corneal microscope (using a Hruby lens or a preset lens). Since these instruments require good cooperation, they can be used only in older children.

It is almost mandatory that the pupils in both eyes be dilated so that satisfactory visualization of the discs may be obtained. It has been my experience that often the margins of the disc might appear fuzzy through an undilated pupil, especially in those with refractive errors (hyperopia and astigmatism), but when the pupils are dilated the discs appear normal. Paradoxically, I have seen the opposite happen in those with little or no refractive error, that is, what appears to be normal through the undilated pupil might prove to be early papilledema after dilatation of the pupil. Either way, it is advantageous to dilate the pupils, for then one can take advantage of parallax displacement to determine elevation of the disc and the fuzziness of the margins as well as to determine presence or absence of venous pulsation. If necessary, the child should be examined under anesthesia or at least mild sedation.

In complete accord with what Rand[9] found in his review of 38 cases, the diagnosis of tumor was either missed or considerably delayed in several instances in this series because the eyegrounds were not examined. An example of this was that of a 6-year-old white girl § admitted with the chief complaint of vomiting over a period of six months. Emaciated almost to the bone, she had been diagnosed by a general practitioner to be suffering from chronic gastroenteritis. Had her fundi been examined, the marked bilateral papilledema would have hastened the neurosurgical work-up. Proper management might have been instituted early and life prolonged.

One should not concentrate on examining the fundi for papilledema alone. One should be on the lookout for optic atrophy as well. Before the eyes are dilated for this purpose, the pupillary reflexes should be carefully checked and the extraocular muscles examined for any evidence of muscle paresis or palsy. Diplopia fields should be done, if possible. An attempt should always be made to elicit nystagmus, bearing in mind that nystagmus at the extreme positions of gaze is normal. An optokinetic drum can be used to advantage in cooperative patients, and comparison of the responses in both eyes is of paramount importance. Whether or not there is evidence of papilledema or optic atrophy, it is imperative that the visual acuity be tested with use of pictures or the letter "E" game in young children and that the visual fields be plotted, at least grossly. The latter is extremely difficult to do, and one may be satisfied with the gross result obtained by moving attractive toys or a muscle light from the side of the patient

§ This patient proved to have ependymoblastoma in the fourth ventricle.

and taking note of how soon the patient's attention is aroused.

Since the incidence of unilateral anesthesia of the cornea is an early finding in cerebellopontine angle tumor,[6] a wisp of cotton should be gently passed on each cornea in all patients where this type of tumor is suspected. The normal response is almost instantaneous blinking and even upturning of eyeball.

The status of the lids (ptosis, lagophthalmus, etc.) and prominence of the eyeballs should be investigated routinely, although exophthalmometry is rarely necessary.

Finally, the role of an ophthalmologist in the diagnosis of brain tumor has to be defined. He assumes two main positions in this regard: first, as a consultant regarding the differential diagnosis of papilledema and optic atrophy and also regarding the status of the extraocular muscles, the visual fields, and so forth; second, as an ordinary doctor, referring patients to the neurosurgeon or the neurologist.|| Before doing this, he might want to refer the patient to the radiologist to strengthen his basis for consulting the neurology specialist.

In the differential diagnosis of papilledema, especially in adults, one encounters greatest difficulty in ruling out papillitis. In both conditions, the nerve heads are elevated, with fuzzy margins, even surrounded by hemorrhages. The veins are engorged, but this may be more pronounced in papilledema than in papillitis. The blind spots are considerably enlarged in both cases. Table 15 depicts the main differential points between the two.

Another condition that can simulate papilledema is congenital pseudoneuritis, which is usually associated with considerable hyperopia.[12] Here, the hyperopia is more significant than the fuzziness of the disc margins, vision may be correctible with lenses, and the blind spots are within normal limits. There are no retinal hemorrhages, no venous engorgement, and no fluctuations in appearance of the nerve head as observed in papilledema and papillitis. The history is suggestive of nothing but visual difficulty early in life.

Persistence of Bergmeister's papilla, proliferation of glial tissue, medullated nerve fibers, and other congenital aberrations, which offer little trouble to ophthalmologist, might appear confusing to the general practitioner and occasionally to the neurologist. In these cases there may be considerable elevation of the disc even to 5 or 6 D. The only visual field finding is an enlarged blind spot.

Again, it is reiterated that since it may be unsafe to do spinal tap on cases with papilledema that ophthalmologist should be consulted in borderline cases. His stock of knowledge regarding both congenital and acquired anomalies of the nerve head is unquestionably richer than that of his colleagues in the other specialties. Although the ophthalmologist does not assume the final say in the diagnosis of brain tumors,

TABLE 15.—*Differential Diagnosis Between Papilledema and Papillitis* *

Differential Points	Papilledema	Papillitis
History	Usually suggestive of increased intracranial pressure; headache, vomiting, etc.	Presence of foci of infection; teeth, tonsils, sinuses, etc.
Onset	Insidious, rarely sudden	More sudden onset
Vision	Preserved in the beginning, but deteriorates later unless condition is relieved.	Loss of central vision in a day or 2; recovery may be complete
Visual fields †		
Early	No central defects	Central defects usual
1-2 wk. later	Preponderance of defective field around blind spot	Around fixation area
Vitreous	No cloudiness	Cloudiness in posterior part
Unilateral or Bilateral	Usually bilateral	Usually unilateral

* Venous engorgement and hemorrhages, as well as elevation, are usually marked in papillitis.

† Chamlin[13], Cordes, and Aikin[11] all emphasize the importance of perimetry and tangent-screen examination in making a differential diagnosis between papilledema and papillitis.

|| Children suspected to have brain tumor should be under the care of a pediatrician, who holds final responsibility. A thorough medical evaluation is absolutely essential, and should be the main basis for further diagnostic and therapeutic planning.

he can help clinch the diagnosis by his knowledge in ophthalmoscopy, in perimetry, in ocular muscles, and in the anatomy of the visual pathways in relation to other parts of the brain.

Summary

The commonest ocular findings in a series of 172 verified brain tumor cases were papilledema, visual field defects, nystagmus, ocular motor palsies, disturbance of the pupillary reflexes, failing vision, and optic atrophy. Less frequent findings were ptosis, corneal anesthesia, proptosis, lagophthalmus, Horner's syndrome, and lid lag.

It is significant that 27 of the 39 patients with papilledema undergoing spinal tap had some elevation in the spinal fluid pressure.

In addition to increased spinal pressure, there are three other evidences in children of increased intracranial pressure, namely, papilledema, suture separation, and dilatation of one or more ventricles. Of the three, the most reliable sign was enlargement of the ventricles.

In the few cases studied, there is reason to believe that abducens palsy is related to increased intracranial pressure, since of all the cranial nerves this nerve has the longest intracranial course.

The course of papilledema varied with the rapidity of the growth of the tumor as well as the location of the tumor mass. Papilledema that has an acute onset is associated with retinal hemorrhages, while the chronic cases tend to wind up with optic nerve atrophy, depending on the degree of the nerve-head swelling.

The differential diagnosis of papilledema is briefly discussed.

The role of the ophthalmologist in the diagnosis of brain tumors is twofold: first, he acts as a consultant regarding eye findings; second, he acts as an ordinary practitioner referring cases to the neurological specialist.

635 S. Westlake Ave. (57).

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An Isopter in the Intermediate Field of Vision

MAX CHAMLIN, M.D., New York

Standard clinical studies of the visual fields provide for determinations of the peripheral field on the perimeter and central fields on the tangent screen. On the perimeter arc, useful clinical isopters have been worked out for as small a visual angle as 1/330 white. These were carefully described by Ferree and Rand[1] in 1931, and formed the basis for the Montefiore charts described by me[2] in 1948. The 1/330 white field, which is the innermost peripheral isopter studied by Ferree and Rand, extends to 64 degrees temporally and 47 degrees nasally. It may well be that in many cases the nasal field does go out as far as 50 degrees and the temporal to even a little better than 65 degrees. As for the tangent screen, isopters can be measured only up to 25 degrees because of the increasing tangential differences producing inaccuracies beyond this limit.

Therefore, since the central field describes clinically useful isopters peripherally only up to 25 degrees and the perimeter describes clinically useful isopters centrally only up to the 50- and 65-degree arcs, this leaves a large area of field between 25 and 50 degrees nasally as well as between 25 and 65 degrees temporally for which a practical clinical isopter is not in general use today. Theoretically, one could define and describe a new isopter on the 330 mm. perimeter arc with a small test object, such as 0.5 mm. white. However, the experienced perimitrist knows that using an 0.5 mm. test object for the peripheral field is quite impractical owing to the difficulty in standardizing the 0.5 mm. test object, whether an actual object or a projected light, as well as in obtaining a good carrier which would not be easily confused with the test object itself. Therefore, for practical purposes, neither the tangent screen nor the 330 mm. perimeter arc is easily adaptable for clinical purposes to describe and utilize an isopter lying somewhere between the two limits described above.

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From the Department of Ophthalmology of the Albert Einstein College of Medicine of Yeshiva University and the Division of Ophthalmology of the Montefiore Hospital.

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Purpose of Studying an Intermediate Isopter

In attempting to discover and describe an isopter in the intermediate field of vision, one need not really have a specific clinical purpose in mind. It is merely sufficient to say that the entire field of vision should be explored for whatever clinical application it may have. This is no less true in the studies of the field of vision than it is in the study of the electrocardiogram or the electroencephalogram, which attempts to describe the functioning of every portion of the heart or brain by various leads.

As a matter of fact, judging by some of the clinical data obtainable in a study of visual fields, there seems to be good reason to believe that there is more than an intellectual curiosity to be satisfied in studying this intermediate isopter. It has been shown that some diseases affecting the visual pathways will, at first, affect only the peripheral field.[3] Conversely, other diseases will affect

the central * fields, leaving the peripheral fields intact. This is particularly true in early chiasmal interference.[4,5]

It seems logical that the large area of field lying between these two limits might well be the site of defect due to other types of interference with the visual pathways. As a matter of fact, there seems to be some clinical evidence that glaucoma and some prechiasmal tumors may first show defects in this intermediate zone. Thus, it is well known to clinicians and investigators in the field of glaucoma that the visual-field changes are certainly among the most important criteria for the evaluation of treatment and the decision as to whether or not to perform surgery. Even tonography may be said to serve as a guide or prognostic sign in anticipation of visual-field changes. At the present time, there is no definite uniformity of opinion as to where such visual-field changes first start. Some say that the elongation of the blind spot comes first, and if this is actually so, it may well represent a contracture in the isopter in the visual field we are seeking to explore, i. e., from 25 degrees to 45 degrees extending inward to involve area caeca. Others say that the central field shows defects first, and still others say that the peripheral field shows them first. It may be that it is really this intermediate field which shows the earliest changes, and the peripheral or central defects described above may be only extensions, either inward or outward, repectively, from this intermediate isopter.

Prechiasmal Tumors

Tumors in the prechiasmal area may start with a peripheral defect if interference with the optic nerve is close to the optic foramen,[3] or the field defect may start with one in the 1/2,000 field or central field if the lesion is nearer to the chiasm.[5] However, on some occasions, while visual field studies on both tangent screen and perimeter fail to show any definite defects with standard techniques, the neurosurgeon finds a tumor compressing the optic nerves somewhere between the optic foramen. It seems inconceivable that such compression should not cause a visual field defect. Since the intermediate area described above has not had any clinically useful minimal isopters worked out, it does seem possible that some mass lesions around the optic nerves may produce field defects first showing up in this intermediate area.

On a more theoretical note, one has only to read through Traquair's description of the choroidal blood supply,[6] wherein he describes an anastomosing choroidal circulation in the posterior half of the choroid and another anastomosing circulation in the anterior half of the choroid, but a lack of such an anastomosis in the choroidal arterial twigs in the intermediate zone. He goes on to say, ". . . [it] has been inferred from this that in certain pathological conditions the circulation in the intermediate zone is more liable to failure than that in the anterior or posterior portion, a view which forms the basis of one of the suggested explanations of the ring scotoma in retinitis pigmentosa."

From the clinical implications mentioned above as to glaucoma and mass lesions, as well as from Traquair's description of the poorly supplied intermediate zone of the choroid, one may conceive of a clinically useful isopter that may be derived from a study of the intermediate field. With this purpose in mind, equipment was designed for such purpose.

Construction of New Equipment to Study Intermediate Field

Since the visual field beyond 25 degrees had to be studied, it was obvious that an arc surface would have to be used in order to avoid the tangential errors introduced by the flat surface. In order to avoid the very small test objects such as 0.5 mm., and yet

* In previous publications, I have referred to the 10 to 20 degree isopter as "intermediate" field. At this time, in order to avoid confusion, it would seem desirable to use this term for the isopter described in this paper and to consider the 10-20 degree area as part of central field.

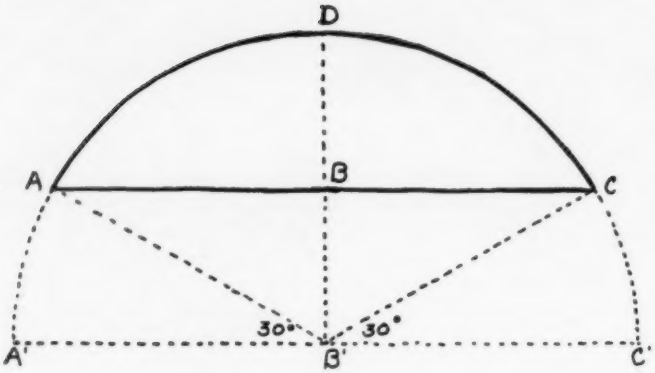


Fig. 1.—Geometric construction of bowl, on radius of 750 mm. Solid lines depict actual bowl, extending to 60 arc degrees all around. *B'D* (750 mm.) represents radius; *B'* corresponds to site of patient's eye; *D* corresponds to width of fixation on bowl; *AC* corresponds to width of bowl (642 mm.); *BD* corresponds to depth of bowl (375 mm.).

utilize a suitably small visual angle for the stimulus, it was also obvious that a radius larger than 330 mm. would have to be used. Therefore, the use of a 1-meter arc was entertained, and such an arc was actually constructed. One does not appreciate fully the amount of space required to rotate an arc of such size until one actually constructs it. This arc was affixed to the wall and rotated through the various meridians to describe the entire field.

The awkwardness involved in manipulating this arc and the difficulty in illuminating it as well as providing a suitable background convinced me that the 1-meter arc was impractical for clinical use, and I therefore decided to have a bowl perimeter constructed with a 1-meter radius, so as to have a fixed area not requiring rotation. Again, one does not fully appreciate the large size of such a piece of equipment until actually faced with it. Consultations were held with various manufacturers, and it was decided to construct this dome-like equipment of plastic material. Considering the size of the bowl, such plastic material was light in weight and provided the least expensive way of constructing it. Since the field being described was not bigger than 55 to 60 degrees temporally, the structure was planned geometrically up to 60 degrees, but even then it became cumbersome for practical use, and it was finally decided to limit the size of the arc to a ¾-meter radius. This was done, and a plastic arc was constructed on a radius of 75 cm., extending up to 60 degrees all around (Fig. 1). This plastic sphere was then lined with black felt, and the arc degrees were marked off every 5 degrees. The entire bowl was mounted on the wall and

Fig. 2.—The bowl perimeter, mounted on wooden frame and hung on wall. The inside of the bowl is lined with black felt. The arc markings are made with a dull black crayon, but, for purposes of this photograph, they were done in white.

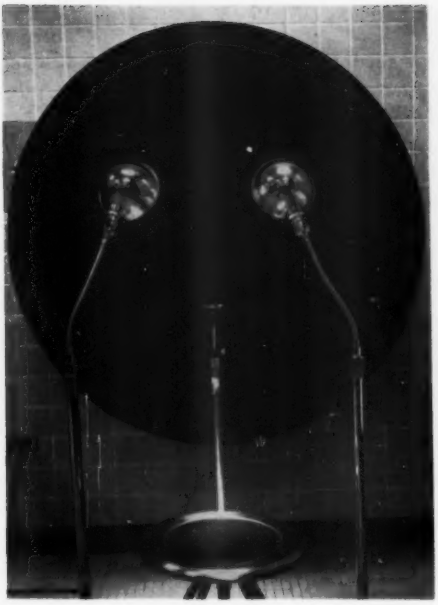


Figure 3

Fig. 3.—The chin rest, foot lamps, and patient's stool in position before the bowl. The chin rest is moved so that the patient's eye is 750 mm. from the fixation point. The inner 20-degree arc is marked off every 10 degrees and the outer arcs every 5 degrees.

Figure 4

Fig. 4.—The felt-covered, pliable plastic carrier is shown. The edges have been outlined with a white string and the 1.3 mm. test object replaced with a larger arc, both for photographic purposes only.

Fig. 5.—The plastic test-object holder is bent easily to conform to concavity of bowl. All white markings as well as the larger sized test object are inserted for photographic purposes only. The pliable band of plastic is affixed to a long, sturdy plastic rod.

Figure 5

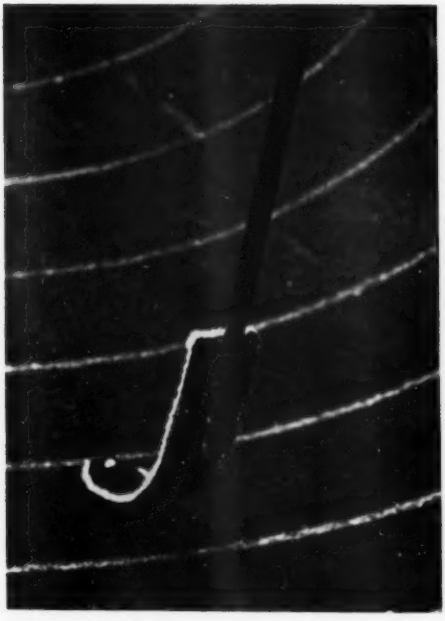


Fig. 6.—Patient in position for examination. The test object is being brought in on the carrier. (Bowl markings and carrier outline are marked off in white for photographic purposes.)

Figure 6

illuminated with two standing gooseneck lamps with 25 watt bulbs which provided fairly even illumination of 8 to 10 ft-c. A chin rest was used for the patient. The next question that came up was that of the size of the test object and the type of carrier (Figs. 2-6).

As for the size of the test object, since it was desired to create an isopter midway between that for 1/330 and 1/2,000 (the latter being one of the better and more accurately measured isopters on the tangent screen), the visual angles produced by these tests were computed and a mean visual angle calculated between them. Thus, the visual angle for 1/330 white corresponds to 10.38 minutes and that for 1/2,000 white to 1.71 minutes. Intermediate between these two is a visual angle of 6.04 minutes. By actual calculation it is found that a 1.3 mm. test object was required at 750 mm. to produce a visual angle of 6.0 minutes, and therefore such a test object was used. To check further on the advisability of a 1.3 mm. test object, several test objects were utilized, some smaller and some larger than 1.3 mm. and it was found by actual use that a 1.3 mm. test object did describe an isopter lying somewhere between 25 and 50 degrees and was readily seen in that area.

In order to find a test object of this size, I merely purchased a large number of so-called "1 mm." plastic spherical test objects. Actually, very few of these so-called 1 mm. test objects were made accurately and, by actual measurement under magnification, some were found to be under 1 mm. and some almost 1.5 mm. By sorting them, we were able to pick practically any size we wanted in this range, and the 1.3 mm. test object was chosen as described above.

In order to find a carrier which would not attract much attention, it was necessary to use a black felt carrier made of the same material as the lining on the bowl. Furthermore, in order to avoid any shadows of such carriers against the background and to conform to the rounded surface, soft plastic material was used which would bend easily with the curvature of the bowl (and thus could be placed flush against the side of the bowl for testing). For this purpose, a piece of easily flexible plastic was covered with some of the black felt material and the small white test object, mounted on its pin shaft, was stuck right through the felt as shown in Figure 4. The entire piece of flexible plastic was then mounted on a sturdier rod of less flexible plastic and thus formed an excellent carrier for the 1.3 mm. test object.

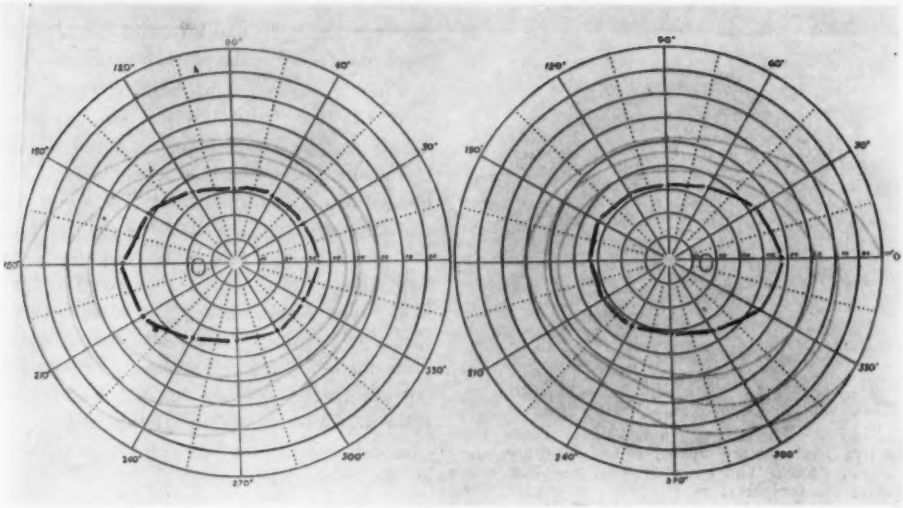
Technique

The patients available for this study were mostly of a young age group, since they

Average Reading for Meridian in Each Eye *

Left		Right				
Meridian	Reading	Reading	Meridian	Difference in Reading	Av. Reading	Nearest Clinical Value
180	48.0	47.6	0	0.4	47.8	48
150	41.9	42.3	30	0.4	42.1	42
120	34.1	34.7	60	0.6	34.4	34
90	31.4	31.5	90	0.1	31.4	31
60	32.1	32.3	120	0.2	32.2	32
30	33.6	33.1	150	0.5	33.3	33
0	34.4	33.4	180	1.0	33.9	34
333	32.3	33.1	210	0.8	32.7	33
300	33.2	32.4	240	0.8	32.8	33
270	32.6	30.5	270	2.1	31.5	32
240	37.2	35.8	300	1.4	36.4	36
210	44.0	43.0	330	1.0	43.5	44

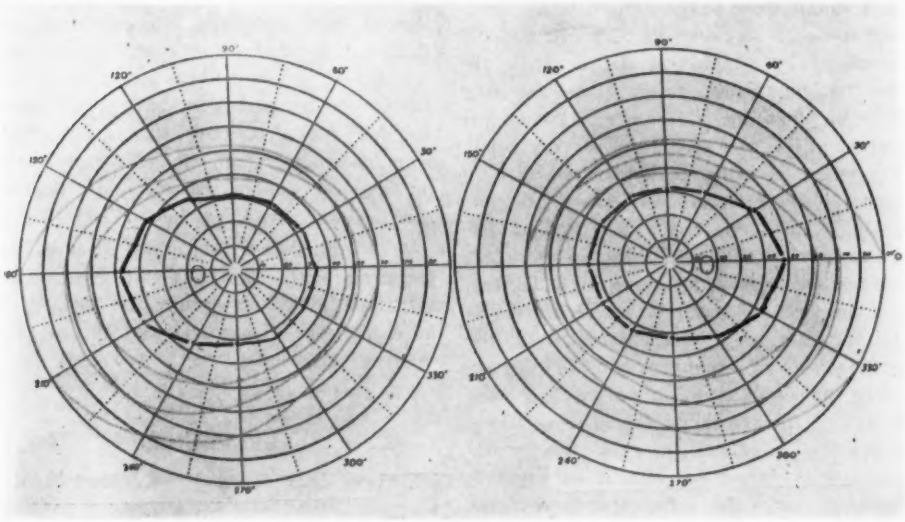
* Average of 62 left eyes for each meridian, average of 59 right eyes for each meridian. The corresponding meridians for right and left eyes are shown side by side, their small differences thus being noted and recorded. The last column represents the average of left and right eyes, thus giving the readings for a reasonable clinical normal isopter for 1.3/750 white.

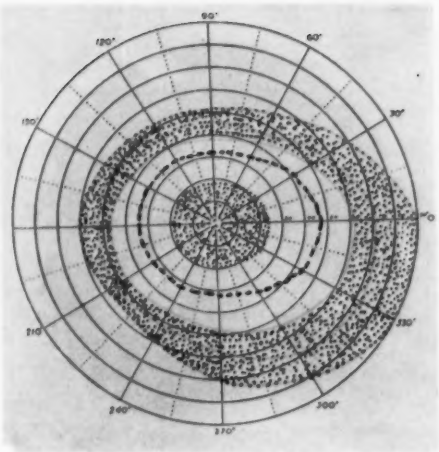


Field 1.—Average normal isopter in 62 left eyes and 59 right eyes for 1.3/750 white.

had to be recruited from the personnel in the hospital. Only those patients were utilized who had normal vision with correction, and where any degree of refractive error was found, the glasses were used in studying their fields. Illumination was obtained as mentioned above and the visual fields recorded every 30 degrees as on any other perimeter. Both eyes were studied in each of 63 patients, whose average age was 27 years. Two persons carried out the examination in all these patients, both of them working together and using the same techniques. Before recordings were entered,

Field 2.—Average of left and right fields, to present a reasonable normal isopter for 1.3/750 white.





Field 3.—The inner stippled area shows the central field usually available for study on the tangent screen. The outer stippled ring-like area shows the peripheral field containing isopters for 5, 3, and 1/330 white, all of which can be studied on the perimeter. The clear zone between them may be labeled the "intermediate field." The broken heavy line in the clear zone represents the normal isopter for 1.3/750 white as found in this study and is seen to lie about midway in the "intermediate zone."

several trial readings were made until there was enough constancy for accurate recording.

Thus, 12 meridians were described in each eye of the 63 patients. Of these, 62 left eyes and 59 right eyes were available and suitable for study. The average reading for each meridian in each eye was determined by simple calculation, with the results shown in the Table. It is interesting to note that the difference between the right and left eye averages was very small. For example, in the 90-degree meridian in each eye the difference was only 0.1 degree, indeed a negligible error. The highest difference was in the 270-degree meridian, where there was a difference of 2 degrees, but this also is a rather small length on the 750 mm. arc. The average of all the differences of the two eyes was 0.75 degree, which corresponds to somewhat less than a ½ in., thus speaking for the accuracy of the results in the two eyes. The actual readings as found are plotted in Field 1. However, since the differences were actually so small, and in order to make a uniform field, the averages were computed between the right and left, and the resultant isopter (1.3/750) is plotted in Field 2.

Field 3 shows a peripheral stippled area, available for study with the perimeter which can be studied for minimal defects by using peripheral isopters, its inner border being delimited by 1/330. The central stippled area describes the field suitable for study on the tangent screen, the outer limits being those of a rather large 1/2,000 field. The large, unstippled area between these two limits comprises the so-called "intermediate field." The heavy broken line represents the average normal isopter for 1.3/750 white as found in this study. As planned, this isopter lies just about midway in the intermediate zone.

Conclusions

The intermediate field of vision, lying between the inner limits of the utilized peripheral isopter and the outer limits of the utilized central isopter, has been discussed as the possible site of early visual-field defects in various disease processes affecting the intra- and extraocular visual pathways.

Since this field does not lend itself to standard equipment for study of minimal defects, new equipment was conceived and designed to study this zone. A 1.3 mm. white test object and a 750 mm. radius bowl type of perimeter have been found suitable for describing this intermediate isopter, which extends to 48 degrees temporally, 34 degrees nasally, 31 degrees above, and 32 degrees below.

It is anticipated that some diseases interfering with the intra- or extraocular visual pathways may show the earliest or most marked visual-field defects in this intermediate zone.

8 E. 77th St. (21)

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Hexokinase of Rabbit Lenses

Effect of Age of Animal

HARRY GREEN, Ph.D., and SHIRLEY A. SOLOMON, B.S., Philadelphia

In previous publications [1] evidence was presented that the relative deficiencies of hexokinase and adenosine triphosphatase in extracts of lenses obtained from young rabbits were limiting factors of the rate and extent of glycolysis. It was further observed that the enzymatic activity of homogenates of young lenses was essentially the same as that of extracts,[2] thereby indicating that the relative deficiences of hexokinase and adenosine triphosphatase did not result from the removal of the enzymes with the readily precipitable particulate cellular debris.[3] Similar conclusions [2] were reached in experiments with homogenates of lenses obtained from 3-year-old rabbits.

Because of the relative deficiency of hexokinase in homogenates of rabbit lenses, the ability of these preparations to produce lactic acid from glucose in an otherwise fortified medium was not very marked. This together with the relatively high concentration of lactic acid present in the lens dictated against achieving a reasonable analytical accuracy in comparing the glycolytic ability of the young and old lens preparations. However, by measuring the rate and extent of production of lactic acid from glucose by homogenates supplemented with crystalline hexokinase and adenosine-5-phosphate, comparative estimates of the metabolic activity of the enzymes in the Embden-Meyerhof cycle beyond that of hexokinase were obtained. Estimates were also obtained by starting with glucose-6-phosphate and fructose diphosphate in the absence of added hexokinase. Comparative studies with young and old rabbit lenses showed that the ability to produce lactic acid from glucose-6-phosphate was markedly higher for the old lens. However, despite an increase in over-all metabolic activity accompanying growth and development of the lens as a unit, the functional metabolic efficiency per unit weight or per unit protein decreased. Moreover, in the two age groups studied, 3-4 weeks and 3 years, the qualitative properties of the lens enzymes associated with the Embden-Meyerhof scheme were not apparently different.

In continuation of the study of the effect of age upon lens metabolism, this investigation was undertaken to compare the activities and other properties of hexokinase in the young and old rabbit lenses.

Materials and Methods

Animals.—The crystal-clear lenses were obtained from pigmented rabbits 3-to-4 weeks old and 3 years old.

Chemicals.—Glucose was Merck's anhydrous, reagent grade. Glucose-6-phosphate, barium salt, was purchased from Schwarz Laboratories, Inc. Chromatographically pure adenosine triphosphate, disodium salt, was obtained from the Pabst Laboratories

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Contribution from the Research Department, Wills Eye Hospital, and the Department of Biochemistry, Graduate School of Medicine, University of Pennsylvania.

Present address of Dr. Green is Smith, Kline & French Laboratories, 1530 Spring Garden St. Present address of Miss Solomon is Philadelphia General Hospital.

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and from the Schwarz Laboratories. All other chemicals employed were of analytical reagent grade quality.

Analytical Methods.—Glucose was determined by the Somogyi [4] method incorporating the suggestions of Colowick, Cori, and Slein.[5] Protein determinations were conducted by the micromethod of Sutherland,[6] with the use of Pro-Sol, standardized protein solution of the Standard Scientific Supply Corporation, as a standard.

Procedure

The lenses were removed and prepared for homogenization as previously described.[1,2] Homogenization was accomplished in glass-distilled H_2O so that 1 ml. of the mixture contained the equivalent of one lens.

For experiments with the component parts of the lens, the entire capsule with the adherent anterior epithelium was stripped off after an incision half-way around the lens along the equator. The material was agitated in distilled H_2O in order to remove some of the adherent cortical fibers,* then blotted dry. The capsule-epithelium tissues were ground in a chilled mortar with increasing small portions of H_2O until four whole capsule-epithelium equivalents were contained in 1 ml. of homogenate. With the young lenses, since no clearly distinct and separable nucleus was discernible, the rest of the lens was homogenized as a whole. With the older lenses, a clearly distinct dense nucleus was separated from the softer cortex and each was homogenized separately, so that the final concentration was one tissue-equivalent of whole lens per milliliter of homogenate.

Experimental Procedure

In general, all incubations were conducted at 37 C in conical centrifuge tubes, each containing a glass rod for occasional stirring during the course of the reaction. Each tube contained homogenate, glucose, and ATP,† the molar concentration ratio of glucose to seven-minute P being 10:1.‡ In addition, all tubes contained 2.5×10^{-2}M NaF, 7.5×10^{-3}M $MgSO_4$, and 2.0×10^{-2}M of buffer. The glucose concentration varied between 1.4×10^{-4}M and 1.7×10^{-3}M.

pH Measurement.—All pH determinations were made with the Cambridge Model L Electron Ray pH meter. Except for the determination of the pH-temperature coefficient, all measurements were made on samples chilled in an ice bath with the temperature correction factor of the instrument set at 10 C, the lowest setting. All adjustments of pH were made with 0.1N NaOH or 0.1N HCl. In all cases the pH of the homogenate-containing mixture was adjusted immediately prior to incubation. For the determination of the pH-activity relationship, citrate buffer was used for pH below 7.0, phosphate-tris(hydroxymethyl)aminomethane (tris) for pH between 7.0 and 8.5, and barbital (Veronal) for pH between 9.0 and 10.0.

Hexokinase Activity.—The relative activity of the enzyme was calculated from the difference between the amount of glucose remaining at the end of incubation and that present at the start. The difference was taken as the quantity of glucose that disappeared as a result of the hexokinase activity of the system. The endogenous reducing sugar present in the homogenates prepared from the young and old lenses was identified as being a ketohexose with paper chromatographic properties similar to those of fructose. In the absence of an exogenous supply of glucose no appreciable decrease in the ketohexose content occurred when the

* Microscopic examination of the washed capsule-epithelium indicated the presence of adherent cortical fibers.

† The following abbreviations have been used: ATP, adenosine triphosphate; seven-minute P, the amount of inorganic phosphate liberated after seven minutes' hydrolysis at 100 C in 1 N HCl.

‡ No attempt was made to determine the optimal ratio of seven-minute P to glucose. In separate experiments, however, it was found that under the experimental conditions of this investigation, the concentration of seven-minute P remained substantially constant when ATP was incubated in the complete system.

otherwise complete homogenate system was incubated for 15 minutes. This experiment indicated that at the concentration of fructose normally present in the lens (about 2μg.-10μg. in young and about 130μg.-150μg. in old lenses) no hexokinase activity with this sugar could be demonstrated. Consequently, the initial concentration of glucose present in the incubation mixture was taken as the amount added. In general, 1 ml. of the pH-adjusted incubation mixture at ice-water temperatures was pipetted into a centrifuge tube and placed in the 37 C bath. Two minutes were allowed for temperature equilibration with stirring, after which the mixture was incubated for the given time period. The reaction was stopped by the addition of 2 ml. each of the $Ba(OH)_2$-$ZnSO_4$ reagents, and the Somogyi procedure was continued.

Results

pH-Temperature Coefficient.—As noted previously, all pH measurements were made under ice-water conditions (3-5 C) so as to suppress any enzyme activity during the preincubation manipulative steps. In view of the fact that all incubations were conducted at 37 C and of the desirability of reporting the data at this physiologic temperature, it was necessary to determine the pH-temperature coefficient for the incubation mixtures prepared from each lens group. The data obtained at 5 degree intervals between 10 and 25 C gave a temperature coefficient of −0.051 pH units per centigrade degree for the young lens homogenate fortified with NaF, $MgSO_4$, and ATP and in a phosphate-tris buffer, pH 8.0 at 25 C. The value for the old lens homogenate under comparable conditions was −0.046. In both cases 0.4 ml. homogenate, representing 40% of a whole lens equivalent, was contained in a total volume of 1.0 ml. The corresponding coefficient for the buffer itself was −0.047.

While the lowest temperature adjustment on the pH meter was 10 C and all pH adjustments prior to incubation were made at 3-5 C, it was nevertheless found that the recorded pH did not change between 5 and 10 C. Consequently, all corrections of pH to 37 C were made from the temperature interval of 10 to 37 C (27 × the temperature coefficient).

Activity as a Function of pH.—Preliminary experiments conducted at pH 8 indicated maximal enzyme activity at an initial glucose concentration of about 1.4×10^{-3}M. Accordingly, the optimal pH for the hexokinase activity of the lens homogenates was determined in the presence of this initial glucose concentration. The reaction time was 15 minutes, and 0.4 ml. of homogenate was mixed with 7.0×10^{-3}M ATP, 2.5×10^{-2}M NaF, 7.5×10^{-3}M $MgSO_4$, and 2.0×10^{-2}M of buffer in a total volume of 1.0 ml. The results showed that the hexokinase activity of the young lens homogenates had a broad optimal pH range between 6.5 and 7.7, and that of the old lens homogenates had a broad optimal pH range between 7.3 and 8.0, at 37 C. It is interesting to note that the pH's of the homogenate preparations themselves, i. e., lenses homogenized in double distilled H_2O were 6.46 and 6.08 at 37 C for the young and old lenses, respectively.

Activity as a Function of Substrate Concentration.—The relationship between the

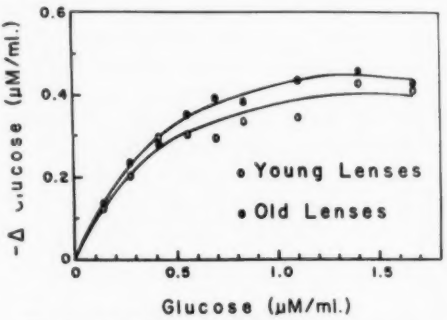

Fig. 1.—Activity correlated with substrate concentration. Incubation mixture: 1 ml. of incubation mixture contained 0.4 ml. of homogenate (0.4 of a lens in H_2O). Final concentrations of additions other than glucose and ATP: 2.5×10^{-2}M NaF, 7.5×10^{-3}M $MgSO_4$, and 2.0×10^{-2}M Tris-phosphate buffer. Molar ratio of 7 min. P to glucose was 10:1. Time of incubation at 37 C was 15 minutes. pH: for young lens systems, 7.3; for old lens system 7.6, corrected to 37 C from measurements made in the cold.

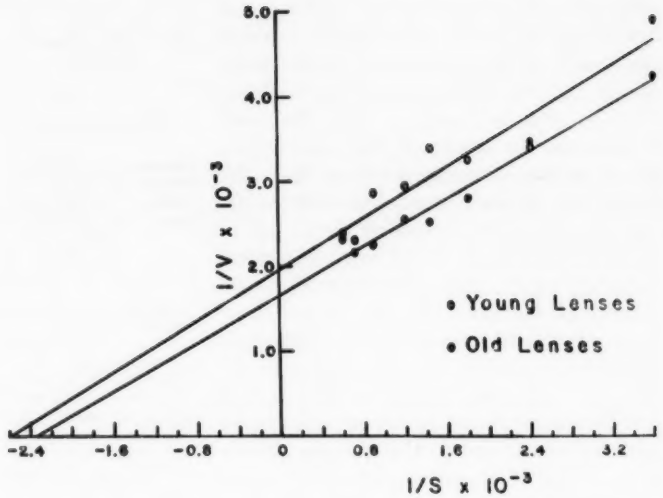

Fig. 2.—Michaelis-Menten plot of data in Figure 1.

rate of hexokinase activity of the complete homogenate systems, measured as the disappearance of substrate (glucose) in 15 minutes at the respective pH optima, and the initial substrate concentration is graphically illustrated in Figure 1. It is apparent from the results, representing typical experiments with 0.4 ml. of homogenate, that the curves are similar for both age-group preparations. The maximal disappearance of glucose was about 0.4μM and occurred at an initial substrate concentration of about 1.2×10^{-3}M.

When the substrate-activity curves were redrawn according to Lineweaver and Burk,[7] straight lines § were obtained as shown in Figure 2, extrapolations of which crossed the abscissa at values of -2.33×10^{3}M and -2.5×10^{3}M, respectively, for the old and young lens preparations. Determination of the Michaelis constants, *Km*, (the intercept of the curve with the $1/S$ axis occurs at the point having the numerical value of $-1/Km$) gave 3.89×10^{-4} for young lenses and 4.29×10^{-4} for old lenses.

Activity as a Function of Volume of Homogenate.—To permit a wider range of volumes of homogenate per milliliter of incubation mixture to be assayed, the lenses were homogenized in a solution containing NaF, $MgSO_4$ and tris-phosphate buffer, instead of adding these substances to the homogenate prepared in H_2O alone, as described above. The final concentrations of ingredients present were the same as in the previous incubation mixtures. No significant difference in activity of the two incubation mixtures was observed. It was found that the amount of glucose that disappeared for both the old and young lens preparations was directly proportional to the volume of homogenate, between 0.2 and 0.8 ml. per milliliter of incubation mixture. The incubations were carried out at 37 C, pH 7.2-7.6, and at an initial glucose concentration of 1.39×10^{-3}M. No detectable amount of glucose disappeared in the absence of homogenate.

Activity as a Function of Time.—With both young and old lens preparations the amount of glucose that disappeared was directly proportional to the duration of the incubation, at least up to 30 minutes.

Activity of Mixture of Young and Old Lens Homogenates Compared to the Separate Activities (Table 1).—In the foregoing experiments the hexokinase activities of young and old lens homogenates containing

§ The best straight lines were drawn by graphical procedures which meet the criteria of the method of least squares.

equal proportions of whole lenses were compared. On the basis of the lens as a whole, the results clearly indicated that the hexokinase activities of the young and old lenses were approximately equal. On the other hand, since the old lenses were, on the average, about four times as heavy as the young lenses, the activity per unit weight for the old lenses was about 25% that of the young lenses. Similarly, since the amount of protein increased proportionately to the weight of the lens, the activity per milligram of protein was less for the old lenses than for the young lenses by the same factor. In order to determine whether any specific inhibitors of hexokinase are formed with advancing age of the lens the activity of a mixture of young and old lens homogenates was compared to each homogenate separately. The results in Table 1 show that the activity of the mixture containing equal parts by volume of the homogenate was the same (within 10%) as the sum of the activities of the same volumes of the separate homogenates.

Activity of Lens of Weight Intermediate Between Young and Old Lenses.—Although the similarity of activities of hexokinase of young and old lenses (when the whole lens is compared) may be fortuitous, in order to determine whether the activity of the whole lens may indeed remain relatively constant throughout the age span studied, the activity of an intermediate weight lens was compared to the values obtained for young and old lenses under exactly the same experimental conditions. The results from one such experiment (homogenate prepared from at least eight lenses, average weight 290 mg.) suggest that the activity of the intermediate weight lens is approximately the same as for the other two age groups studied.

TABLE 1.—*Hexokinase Activity of Combined Homogenates from Young and Old Lenses*

	Young	Old	Young + Old
Activity *	101.8	116.5	121.7

* Activity of a whole lens equivalent in terms of micrograms of glucose disappeared. Average weight of six young lenses homogenized, 97.8 mg.; average weight of six old lenses homogenized, 546.7 mg. One milliliter of incubation mixture contained 0.6 equivalent of whole lens; for mixture of young and old: 0.3 ml. of each homogenate used, equivalent to 0.3 of each lens. Other ingredients present, final concentrations were glucose, 1.11×10^{-4}-1.39×10^{-3}M; ATP (7 min. P) 5.55×10^{-4}-6.95×10^{-3}M; NaF, 2.5×10^{-3}M; $MgSO_4$, 7.5×10^{-3}M; PO_4-Tris buffer, 2.0×10^{-3}M; incubation conducted at 37 C for 15 min. at a pH of 7.5.

TABLE 2.—*Distribution of Hexokinase Activity in the Lenses of Young and Old Rabbits*

Lens Age	Lens Tissue	Activity *	Protein, Mg.	Activity, per Mg. Protein	Wet Weight, Mg.
Young	Caps. + epi.†	8.5	0.060	142	2 †
	Cortex + nucleus	135.9	36.2	3.8	114 0
Old	Caps. + epi.†	13.8	0.583	23.7	6 ‡
	Cortex	160.5	82.3	1.95	322.0
	Nucleus	0.0	89.3	0.0	230.9

* Activity of whole lens equivalent in terms of micrograms of glucose disappeared.

† Entire capsule with adherent epithelium.

‡ Approximate weights.

One ml. of incubation mixture contained 0.4 ml. of homogenate and glucose, 1.3×10^{-3}M; 7 min. P of ATP; 6.0×10^{-3}M; NaF, 2.5×10^{-3}M; $MgSO_4$, 7.5×10^{-3}M; PO_4-Tris buffer, 2.0×10^{-3}M. Incubation was conducted at 37 C for 15 min. at a pH of 7.3-7.5. The tissue homogenates contained four capsule-epithelium structures per milliliter or one cortex or one nucleus or a combination of both.

Distribution of Hexokinase Activity in Lens (Table 2).—The results of one experiment show that on the basis of the whole lens as a functional unit of growth and development less than 10% of the total hexokinase activity is present in the capsule-epithelium structure of both young and old lenses. The bulk of the activity was found in the lens substance and, in the case of the old lens, this was present in the cortex, the denser nucleus having been devoid of any measurable activity.

Comparison of the activities of the lens substance (cortex + nucleus) of young and old lenses revealed essentially similar values, within experimental error. It should be observed, however, that while the old lens contained a grossly distinct and separable firm, cohesive, and sticky nucleus, in the young lens the substance was uniformly soft and gel-like in consistency and not grossly distinguishable or separable into a cortex and nucleus. Although the measurement of the activity of the cortical and nuclear sections

could be made with reasonable accuracy, the relatively slight activity of the capsule-epithelium structures in the presence of large amounts of substrate made the measurements with the latter structures subject to rather large uncertainties. Therefore, quantitative inferences from the data with the capsule-epithelium structures are not justified.

It appears safe to say, however, that while the activity of the capsule-epithelium structures represented less than 10% of the total hexokinase activity of the lens, their specific activity was appreciably higher than that of the rest of the lens.

Additional Observations. — Preliminary experiments designed to test the effect of some substances upon the hexokinase activity of the lens showed that 1×10^{-3}M iodoacetic acid inhibited the activity 43% and 1×10^{-2}M inhibited it 51%; 1×10^{-2}M alloxan had no appreciable effect.

Comment

It had already been shown that in the two age groups of rabbits studied, the qualitative properties of the enzymes responsible for the conversion of glucose-6-phosphate to lactic acid were not apparently different. The results of the present investigation, showing the similarity of the respective Michaelis constants and good agreement of the respective pH optima || for the glucose-hexokinase reaction, suggest that the aging of the lens had no apparent effect upon the functional properties of the hexokinase.

An insight into the enzymatic factors that may play a significant role in controlling the metabolic activity of the lens may be gained by a comparative evaluation of hexokinase activity with the activity of the other enzymes of the Embden-Meyerhof scheme. Previously it had been found that the capacity of the whole lens homogenate to metabolize glucose-6-phosphate and generate energy therefrom increased considerably (about 150%) with advancing age of the organ. The present observations, however, indicate that the hexokinase activity of lens homogenates remained substantially constant with advancing age. In view of the primary positional role that hexokinase plays in the sequence of events describing the metabolism of glucose in the lens, it is particularly significant that, in addition to the enzyme being relatively deficient in the normal rabbit lens, its activity does not increase with advancing age of the organ. Enzymatically speaking, therefore, it may be concluded that the capacity of rabbit lens homogenate to metabolize glucose under anaerobic conditions is fundamentally limited by its hexokinase activity and that this metabolic capacity does not change significantly with age of the lens.

The foregoing discussion was developed from the viewpoint of considering the whole lens as a unit of activity, growth, development, and function. Reevaluating these properties on the basis of unit weight or protein concentration leads to a different orientation. The old lenses used in this study series weighed about four times as much as the young lenses, and their protein content was proportionately higher (no change in protein concentration with age). Accordingly, although the capacity of the lens homogenate to produce lactic acid from glucose-6-phosphate increased more than twofold with age, the metabolic activity per unit weight or per milligram of protein decreased markedly. Similarly, although the total hexokinase activity remained constant with age, the activity per unit weight or per milligram of protein decreased to 25% of its original level. Since more than 90% of the total weight of a rabbit lens is composed of H_2O and protein, the latter representing about 30%, it is obvious that as the lens grows and develops, the increase in protein content is not accompanied by a proportionate increase in hexokinase activity or in the activity of the other enzymes of the Embden-Meyerhof scheme for carbohydrate metabolism.

|| The small difference in range between the optimal pH for the homogenates of the two lens groups is probably a reflection of the effect of the different ionic strengths of the environments as well as of the different amounts of total protein in the two systems.[8]

An approach to the understanding of the sequence of metabolic changes that occur during the growth and development of the lens may be made by a study of the biochemical properties of the component sections of the lens. It is apparent from the results in Table 2 that more than 90% of the total hexokinase activity of the lens is present in the lens substance and only a relatively small amount is present in the capsule-epithelium section. It is further apparent that the dense central core, the nucleus, of the lens is devoid of enzymatic activity, while the overlying softer substance, the cortex, contains the bulk of the activity. This distributional enzymatic relationship may be correlated with the growth pattern of the normal lens. Thus the cortical layer is composed of lens fibers laid down by cell proliferation at the equator of the lens. The closer to the center of the lens the older the fibers become. Indeed, as the fibers approach the center they undergo fragmentation with loss of cell nuclei and become compressed into the dense hard core of the lens nucleus. It is reasonable to assume that the cortical fibers contain the complete enzymatic apparatus necessary for carbohydrate metabolism and that the enzymatic activity is destroyed when the fibers disintegrate into the nucleus of the lens. Similarly, the relatively small amount of enzymatic activity of the capsule-epithelium is undoubtedly related to its relatively small bulk compared to the rest of the lens.

Yet it may be argued that despite the relatively small amount of activity in the capsule-epithelium, the activity per unit weight or per milligram of protein (Table 2) was much higher than in the cortex, suggesting that the higher concentration of enzyme activity in this section signifies a greater contribution to the carbohydrate metabolism of the lens. That this conclusion is not compatible with the available data can be shown by a comparison of the results of this study with the data from lens tissue culture experiments. According to Wachtl and Kinsey,[9] a rabbit lens in tissue culture metabolizes about 6 mg. of glucose in 24 hours. The present data indicate that a whole lens homogenate can metabolize about 18 mg. of glucose in 24 hours. The latter value is based upon optimal conditions in a well-fortified in vitro system and may therefore represent the maximal potential for a lens, which undoubtedly does not obtain in vivo. In any event, on the basis that the hexokinase activity of the capsule-epithelium section represents 10% of the total hexokinase activity, it is readily apparent that the contribution of this part of the lens to the utilization of glucose by the living organ is probably minimal.

In this connection, it is worth commenting upon the recent experiments of Harris and co-workers[10] which led to the conclusion that "glucose does not enter the lens solely by simple diffusion but also by some active process involving metabolic mediation," and "one site or barrier at which this process occurs lies at or in close proximity to the lens capsule." The two major metabolic pathways for the enzymatic utilization of glucose, namely the glycolytic and oxidative shunt pathways, both depend fundamentally upon the conversion of glucose to glucose-6-phosphate by the hexokinase reaction. Because of the preeminence of this reaction in carbohydrate metabolism, considerable attention has been directed to its role in the transfer of glucose across biological barriers into tissues and cells. For many years it was believed that the hexokinase reaction was responsible for the active transport of glucose across the intestinal wall. However, Sols[11] on the basis of studies of the substrate specificity of the hexokinase of intestinal mucosa concluded that this enzyme can not participate directly in the active transport of glucose across the intestine.

Unlike the transfer of glucose across the intestine the transfer of glucose into the lens apparently occurs down a concentration gradient,[10] and ordinarily one might conclude from this that glucose enters the lens by a passive diffusion mechanism. However, the studies of Müller[12] and of Harris,[10] showing a decreased uptake of glucose

by the intact lens poisoned with NaF or iodoacetic acid, suggest the operation of an active metabolism facilitating glucose transfer, although the participation of diffusion has been noted by Harris.

To what extent these two mechanisms operate to regulate the transfer of glucose into the lens is at present not known. The fact that in Harris' experiments the uptake of glucose of an incised capsule was decreased only 17%, without any diminution in the amount of reducing sugar accumulated in the lens, suggests that the capsule-epithelium structure plays only a relatively small part in both the absorption and utilization of glucose. Also, on the basis of the observations of Dische and Ehrlich [13] on the ability of bovine lens capsule to metabolize glucose and the results of the present investigation with rabbit lens capsule-epithelium, it is probable that the hexokinase of the lens surfaces fundamentally serves to initiate carbohydrate metabolism for the surface structures own needs.

The aforementioned observation that the reducing sugar content of the lens can be quantitatively accounted for as a ketohexose with paper chromatographic properties identical with those of fructose has important implications relative to the mechanism of glucose transfer and carbohydrate metabolism in the lens. As far as the authors are aware this represents the first differential analysis of the reducing sugar in this tissue, which up to now has been assumed to be chiefly glucose.[10] This is all the more interesting in view of the finding [14] that glucose (about 125 mg. %), identified by paper chromatography, represents the predominant bulk of the reducing sugar present in the aqueous humor of normal rabbit eyes, while less than 10 mg. % of a ketohexose ¶ could be measured.

¶ The ketohexose was determined by the method of Roe.[15] However, it is possible that the relatively large amount of glucose present gave a false-positive test. Consequently, this value is considered to be maximal. Paper chromatographic analysis revealed the presence of glucose only.

The anomalous disparity between the absence of glucose in the lens and the considerable quantity in the aqueous humor bathing that tissue suggests at least one or both of the following possibilities: 1. Glucose is utilized as rapidly as it enters the lens. 2. The glucose molecule is altered on its transfer into the lens. With respect to the first possibility, it is conceivable that the capsule and epithelium of an intact living lens utilizes glucose and this metabolic ability is governed chiefly by the rate with which the glucose comes into contact with these structures and the concentration of the essential enzymatic system. If unchanged glucose is the primary form in which the sugar is transferred across the membrane of the lens and into the cortex, where the bulk of the glycolytic activity of the lens resides, it is difficult to understand why an appreciable amount of glucose could not be found in the homogenates prepared from the lens. On the other hand, the second possibility above provides an explanation by postulating that all or part of the glucose entering the lens is modified and that the resulting altered glucose molecule is the form in which the sugar is transferred into the cortical fibers. Consistent with the present analytical findings is the further consideration that the altered glucose molecule could be the primary substrate for carbohydrate metabolism. It is, of course, recognized that while the first possibility described alone may apply to the epithelium and capsule, the second may be characteristic solely of the rest of the lens.

Regarding the nature of the process of the transfer of glucose into the lens one suggestion is a carrier-glucose complex, perhaps similar to that discussed by Le Fevre [16] for the human red cell but capable of operating in assembly-line fashion into the interior of the lens.

Another consideration arises out of the disproportionate distribution of glucose between the aqueous humor and the lens and the finding that fructose is the reducing sugar present in the lens. This circumstance suggests that fructose may be the funda-

mental substrate for lens metabolism and that glucose is converted into fructose at the surface of the lens. However, because of the relatively low rate of activity of hexokinase in the presence of fructose in concentrations equal to that of glucose in the aqueous humor,[9,14] this possibility appears unlikely, although Wachtl and Kinsey[9] have shown that rabbit lens in tissue culture is capable of metabolizing significant quantities of fructose. The presence of fructose conceivably could come from an isomeric transformation of glucose,[17] if not from a fructose-6-phosphatase. On the other hand the absence of competitive inhibition between glucose and fructose in the experiments of Wachtl and Kinsey suggest the presence of a specific fructokinase as well as a glucokinase. In preliminary experiments,[14] we have found that fructose in concentrations similar to those used for glucose (about 1.4×10^{-3}M) did not elicit very marked hexokinase activity in lens homogenates, but the activity increased slowly with increasing concentrations of fructose. If a specific fructokinase is present in the lens, then before drawing conclusions regarding the activity and affinity of this enzyme towards fructose it is necessary to study the relative stability of the enzyme under the conditions of homogenization employed in the experiments. Of equal fundamental importance would be studies on the substrate specificity of the hexokinase activity of lens homogenates.

Summary

The hexokinase activity in homogenates of young and old lenses was compared with use of glucose as a substrate.

The optimal pH range of activity for the young lens was 6.5-7.7 and for the old lens, 7.3-8.0, corrected to 37 C.

The affinity or Michaelis constants were 3.8×10^{-4} and 4.29×10^{-4} for young and old lenses, respectively.

The hexokinase activity of the lens as a whole remained substantially unchanged with advancing age. Since the old lens was about four times as heavy as the young lens and also contained about four times the amount of protein, the activity per unit weight or per protein concentration decreased very markedly.

More than 90% of the activity was present in the lens substance and less than 10% in the capsule and epithelium. The dense hard nucleus of the old lens was devoid of activity.

The reducing sugar content in lens homogenates was identified as a ketohexose with chromatographic properties similar to those of fructose.

The significance of these findings is discussed relative to the growth and development characteristics of the lens and to the mechanism of transport of glucose into the lens and its utilization.

Caroline A. Hamblin gave technical assistance.

Smith, Kline & French Laboratories, 1530 Spring Garden St.

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Unilateral Retinitis Pigmentosa with Glaucoma

ALEX E. KRILL, M.D., and GILBERT ISER, M.D., Chicago

Retinitis pigmentosa or primary pigmentary degeneration of the retina almost always appears as a bilateral disease and very rarely as a unilateral process.

Pedraglia, in 1865, reported the first unilateral case, and 50 years later Leber could only find 14 cases in the literature. In subsequent reviews of the literature for "authentic" cases Biegelman,[1] in 1931, could only find ten; Dreisler,[2] in 1942, sixteen; Maeder and Muller,[3] in 1950, sixteen; François and Verriest,[4] in 1952, twenty-three, and François,[5] in 1958, twenty-five. All of these authors added at least one case of their own.

The patient to be discussed is of interest because electroretinographic studies have been reported only in two cases [4,6] and associated glaucoma has not been previously mentioned in unilateral retinitis pigmentosa.

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From the Department of Ophthalmology, University of Illinois College of Medicine, and Illinois Eye & Ear Infirmary.

Report of a Case

A 48-year-old white woman was first seen in 1939 for a routine eye examination. Other than the patient having moderate hyperopia, the examination was not remarkable. She was refracted on several other occasions up until February, 1943. During this period the patient's corrected visions varied from 20/20 to 20/30 in the right eye and 20/40+ to 20/50+ in the left eye.

The patient was not seen again until Oct. 1, 1956. At that time she gave a six-month history of intermittent right ocular pain, right frontal headaches, a decreased field of vision with the right eye, and difficulty seeing at night with this eye. There were no symptoms attributed to the left eye. There was no history suggesting syphilitic disease, trauma, or the onset of ocular symptoms in relation to viral or bacterial diseases. The family history was negative for night blindness, known ocular diseases, or consanguinity.

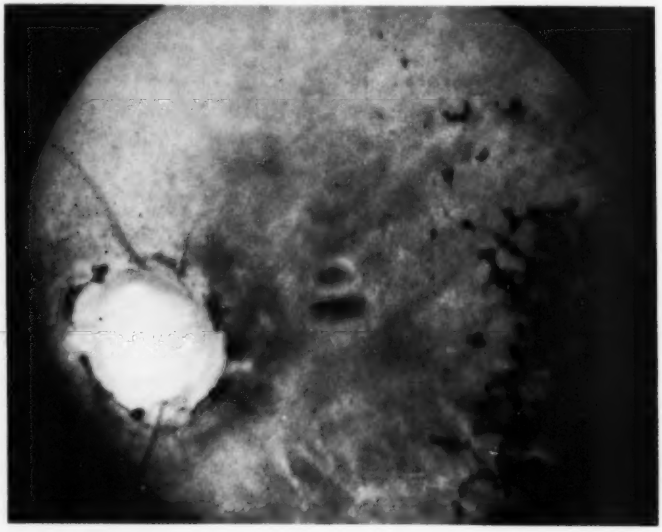

Fig. 1.—Fundus, right eye. Glaucomatous atrophy of disc, attenuation of the vessels, and bone-spicule pigmentation are prominent features.

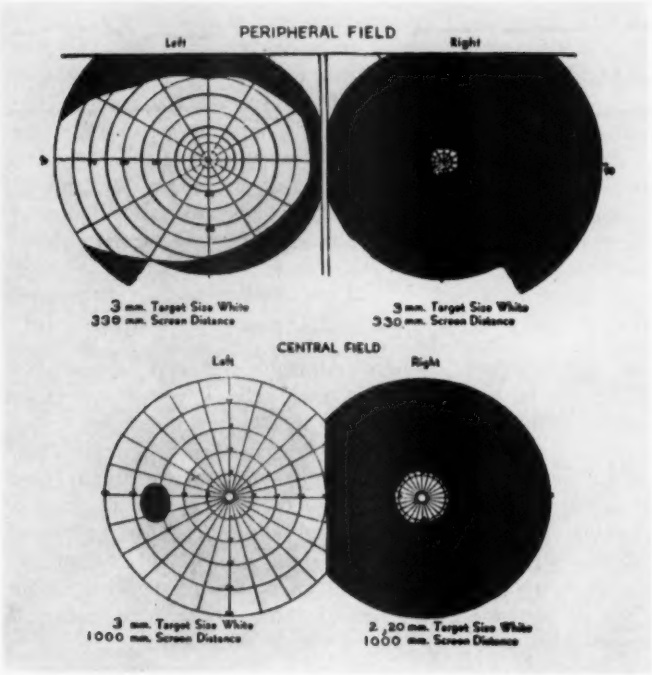

Fig. 2. — Central and peripheral fields. Right eye shows less than 5 degrees of field. Left eye is normal.

The results of the examinations of the right eye upon initial and subsequent visits were as follows: Visual acuities of 20/50 to 20/70 were noted on numerous occasions. Tensions of 15-58 were noted. Posterior polar cataractous changes were seen in the lens. The fundus (Fig. 1) revealed changes which included cupping of the disc with advanced glaucomatous atrophy, attenuation of the arterioles, and bone-spicule pigmentation of the midperiphery. No evidence of old or recent patches of chorioretinitis were seen. Central and peripheral fields were constricted to less than 5 degrees (Fig. 2). Gonioscopy revealed almost 2/3 of the angle filled with synechiae extending to the top of the pigmented trabeculae. A monocular dark adaptation curve * revealed a very elevated monophasic response (Fig. 3) in contrast to the normal biphasic cone-rod response which is depicted by that of

* A complete discussion of the techniques of electroretinography and adaptometry used can be found in previous articles.[8-10]

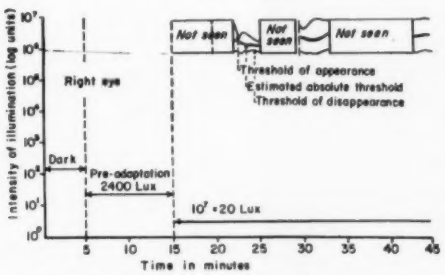

Fig. 3.—Monocular dark adaptation curve of right eye (eccentric 11 degrees). A very elevated monophasic response is seen at short intervals.

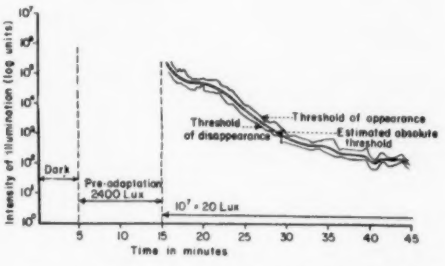

Fig. 4.—Monocular dark adaptation curve of left eye (eccentric 11 degrees). A normal biphasic cone-rod response is illustrated.

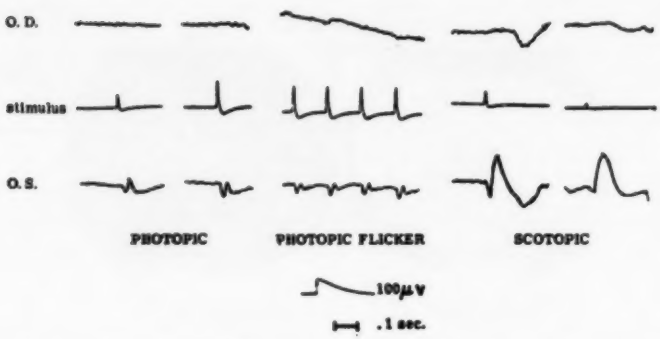

Fig. 5. — Electroretinogram of both eyes. No response is seen for the right eye. The left eye is normal.

the left eye (Fig. 4). The electroretinogram was extinguished (Fig. 5) in the right eye, whereas it was normal in the left eye (Fig. 5).

The left eye did not reveal any significant findings. A visual acuity of 20/20 was noted. Illustrations of the fundus (Fig. 6), visual fields (Fig. 2), dark adaptation curve (Fig. 4), and electroretinographic response (Fig. 5) of the left eye demonstrated some of the more important normal examinations. Gonioscopic examination revealed easily seen pigmented trabeculae throughout the entire angle. In an attempt to provoke glaucoma in the left eye, mydriatics were used on two occasions. In the first test gonioscopy and tonometry were performed before and up to two hours after dilation. Although the angle appeared to be almost completely obliterated except for a few small areas where pigmented trabeculae could be seen, the pressures did not surpass 13 mm. of mercury at any time. In an attempt to perform a more sensitive test for angle-closure glaucoma,[7] tonography was done before and 90 minutes after the administration of mydriatics. The coefficient of outflow (c) varied from 0.27 to 0.31 on the second recording.

The general work-up including all laboratory tests, skull x-rays, and electroencephalogram was normal.

Comment

In an analysis of this case, one must consider the following possibilities. This is

Fig. 6. — Fundus, left eye. Normal appearance is shown.

a case of glaucoma in the right eye with either (1) an associated secondary pigmentary degeneration, (2) an associated retinitis pigmentosa manifest in the right eye which has not yet become manifest in the left eye, or (3) a true unilateral retinitis pigmentosa. It is felt that the first two possibilities are excluded by the following considerations, based on previous experience with electroretinography and adaptometry:

A. Electroretinography.—1. Glaucoma itself should not cause any significant alteration in the electroretinographic response which is dependent only on the intactness and proper functioning of the external layers of the retina.[11,12] Normal electroretinograms have even been recorded in blind glaucomatous eyes.[12]

2. In secondary pigmentary degenerations the electroretinogram is usually reported to be normal or subnormal.[5,11,13,14]

3. The experience of workers with the electroretinogram in retinitis pigmentosa has been to find most often a completely extinguished response even in early cases[5,11,13-18] or very rarely a minimal deflection[14,17-20] or subnormal response.[10,21] Thus an early retinitis pigmentosa in the left eye is unlikely.

B. Adaptometry.—1. Mandelbaum has shown that dark-adaptation studies in patients with glaucoma reveal elevated thresholds which are nevertheless biphasic.[22] This finding was substantiated in a patient with glaucoma that had 20/30 visual acuity and a visual field of 3 degrees in the tested eye (Fig. 7).

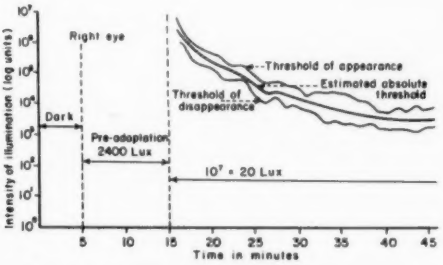

Fig. 7.—Monocular dark adaptation curve (eccentric 11 degrees). This patient has long-standing wide-angle glaucoma with a visual field of 3 degrees in tested eye. Compare this curve with the one in Figure 3.

2. The finding of a normal or an elevated but biphasic type of dark-adaptation curve is the usual finding in secondary pigmentary degeneration or chorioretinitis.[5,14,22] The curve illustrated here for the right eye is more typical of retinitis pigmentosa, which can be frequently characterized by an elevation of the cone threshold and a large contraction or disappearance of the rod portion of the curve.[22]

3. A normal adaptation curve, as shown by the left eye, is unusual if this were an early retinitis pigmentosa, since most of these patients have an early history of night blindness[13,23] and thus may frequently show changes in the dark-adaptation curve as an early finding.

This patient demonstrates features which are similar to other reported cases. A posterior polar cataract was frequently noted in both Dreisler's[2] and François'[4] tabulations of unilateral retinitis pigmentosa cases. A late age of onset was not unusual,[4,5] in contrast to bilateral cases, and there was usually no family history of consanguinity or ocular diseases.[3-5]

The exceptional feature in this instance, the associated glaucoma, is not rare in bilateral retinitis pigmentosa.[24] Sugar states that the association of glaucoma is apparently greater among patients with retinitis pigmentosa than in those without it. All types of glaucoma have been reported with retinitis pigmentosa. Carroll[25] refers to an incidence of 1%-3% in cases of retinitis pigmentosa.

Summary

A case of unilateral retinitis pigmentosa with associated glaucoma is presented.

The importance of electroretinography and adaptometry in the diagnosis of such a case is discussed.

840 S. Wood St. (12).

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The Effect of Prednisolone upon the Absorption of Hyphema in Rabbit Eyes

H. E. MARTINEZ-ROIG, M.D., and GAYLORD W. OJERS, M.D., Philadelphia

Benedict and Hollenhorst have reported that subconjunctivally administered cortisone delays the absorption of hyphema in rabbit eyes. Although a definite difference was found in the rates of absorption in the treated and untreated animals, so few eyes were used (four eyes each for the control and noncontrol series) that it seemed worth while to repeat this experiment in a larger number of animals. Since these authors noted some physical irritation secondary to the subconjunctival injection of cortisone, intramuscular injections were made in our series. Clinically, prednisolone * is now more frequently used by us than cortisone; therefore prednisolone was used in the present experiment.

Procedure

Adult white rabbits were anesthetized with open-drop ether. From the marginal ear vein, 0.4 cc. of blood was withdrawn in a tuberculin syringe with a 25-gauge hypodermic needle. The right eye was then proptosed and grasped at the limbus with a fixation forceps. The anterior chamber was entered obliquely just within the limbus. Aqueous escaped as this procedure was carried out. As soon as the bevel was completely within the anterior chamber, 0.2 cc. of blood was injected and the needle withdrawn. Withdrawal was accompanied by some seepage of blood and aqueous. The identical procedure was then carried out on the left eye.

This procedure was performed binocularly in a total of 20 rabbits. All animals received 0.5 cc. of Dicrysticin † intramuscularly daily for five days. The 10 rabbits used as controls received no additional medications. The remaining 10 rabbits received 2 mg. of prednisolone per kilogram of body weight intramuscularly daily for the duration of the hyphema.

The rabbits were observed daily for hyphema-clearing. In a few rabbits the bulk of the hyphema cleared to a point where a small, organized clot remained either on the corneal endothelium at the puncture site or on the lens capsule. This clot would remain unchanged for long periods of time. It was disregarded on estimating the duration of hyphema in that eye.

Duration of Hyphema (0.2 Cc.)

Control			Experiment		
Rabbit No.	O. D.	O. S.	Rabbit No.	O. D.	O. S.
1	9	15	1	23	26 *
2	32	20	2	26	30
3	12	26	3	41	41
4	18	30	4	20	28
5	23	9	5	41 *	40
6	19	32	6	31 *	31 *
7	37	26	7	36	39 *
8	22	10	8	18 *	18 *
9	15	21	9	38 *	38 *
10	11	--	10	32 *	32 *
Average duration of hyphema 20.3 days			Average duration of hyphema 31.4 days		

* Eyes marked thus were not completely clear at the time o death of the animal.

Seven rabbits died prior to clearing of hyphema, from side effects of Meticortelone.

Results and Comment

The results of these experiments leave little doubt that systemically administered

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* The prednisolone (Meticortelone) used in these experiments was furnished by the Schering Corporation, Bloomfield, N. J.

† Crysticillin (penicillin G procaine) fortified 400,000 units with dihydrostreptomycin sulfate 0.5 gm. for aqueous injection, furnished through the courtesy of E. R. Squibb & Sons, Division of Olin Mathieson Chemical Corporation, New York.

prednisolone delays the absorption of blood from the anterior chamber in rabbit eyes.

Technically these experiments leave much to be desired. The amount of blood remaining in the anterior chamber at the end of the injection varied from eye to eye, not only because 0.2 cc. is only grossly measured in the syringe but also because of the variable amount of leakage from the anterior chamber during the withdrawals of the needle from the cornea. The end point of observation was also difficult because of the tendency for small clots to remain grossly unchanged for long periods of time. A number of rabbits died before the complete absorption of the hyphema in the treated group, presumably from the long continued administration of prednisolone. Had these animals lived, the final conclusion would have been unaltered except that the average duration of the hyphema would have been even longer in the treated animals.

The obvious inference from these experiments would be for the clinician to use the corticosteroid drugs cautiously when blood is present in the anterior chamber. However, it must be remembered that these experiments were carried out in rabbits; furthermore, the doses of prednisolone were larger than are generally used clinically. Accurate clinical observations are needed. In our own cases of traumatic hyphema we have not been impressed that systemic corticosteroid therapy did materially interfere with the usual rapid absorption of the hyphema. Finally, although it may be proved clinically that hyphema is more slowly absorbed in patients under corticosteroid treatment, the question must be raised whether it is better to have faster absorption of blood from a highly irritated eye or a slower rate of absorption from a less irritated one.

Conclusion

Prednisolone given systemically delays the absorption of hyphema from the anterior chamber of rabbit eyes. This confirms the work of Benedict and Hollenhorst. Assuming that this can be applied to man, it is concluded that corticosteroid drugs should be used cautiously when blood is present in the anterior chamber from any cause.

Department of Ophthalmology, University Hospital, 3600 Spruce St. (4).

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Leptospiral Uveitis

ROBERT M. STURMAN, M.D.; JOSEPH LAVAL, M.D., and VICTOR J. WEIL, M.D., New York

The occurrence of uveitis as a complication of systemic Leptospirosis was reported in Weil's [1] original article describing the disease in 1886. The etiologic agent of Weil's disease is ordinarily the Leptospira icterohemorrhagiae, a spirochete found commonly in rats and less frequently in dogs, mice, cats, and other animals. Human infection generally stems from contact with stagnant waters contaminated by murine excreta, the portal of entry usually being the abraded skin, although infection may occur by way of the gastrointestinal tract, the nasal mucosa, or the conjunctiva. The disease is especially prevalent in those working in rat-infested environments: sewer workers, fish and poultry handlers, miners, butchers, tunnel diggers, and others. Systemically, the disease is characterized by sudden onset, with headaches, fever, prostration, and myalgia. In the more severe cases, jaundice occurs and hemorrhagic phenomena and evidences of renal impairment are present. Hanno and Cleveland [2] reported, in 1949, 222 documented cases from the American literature in which uveitis had developed as a late manifestation of the disease.

Diagnosis may be definitely established by the isolation of the causative organism in the blood or urine and by the demonstration of specific lysins and agglutinins in the serum. A positive agglutination in a titer of 1:300 or above or a complement-fixation titer of 2 units or more is considered diagnostic of Weil's disease.

A mild form of iritis or iridocyclitis frequently occurs late in the disease, appearing between the 16th and 42d day. The frequency with which the anterior uveal tract is affected is variously reported as from 3% to 44%. The posterior uveal tract is occasionally involved as well.

Alexander, Baer, Fair, Gochenour, King, and Yager,[3] all of the United States Army Medical Corps, review most of the knowledge of Leptospiral uveitis available in 1952 and present a bacteriologically verified case of the disease. They point out that ocular manifestations have been observed in man as sequelae of Canicola fever, Swineherd's disease, mud (swamp) fever, Japanese seven-day fever (nanukayami), leptospirosis australis B, and Palestine bovine leptospirosis. The variation in ocular involvement, reported varyingly as from 10% to 40%, is interpreted to reflect differences in the intensity of search for ocular manifestations. Alexander et al.[3] point out that ocular involvement may appear as early as the second week of illness or as late as one year after systemic manifestations. In the majority of cases recorded, iritis, iridocyclitis, and chorioretinitis appeared between the first and the sixth month after systemic infection. In the case which they report, infection resulted from a laboratory accident in which leptospirae were splashed upon the face and left eye. The incubation period was 12 days. Laboratory diagnosis was first confirmed by blood culture prior to the patient's antibody response. Coexistence of living pathogenic leptospirae, nesting in the aqueous fluid of the eye, and of high serum antibody levels was established. Woods [4] pointed out in his classic work, "Endogenous Uveitis," that, since leptospirae may remain viable in the pelvis of the kidney long after they have disappeared from the blood stream, it has been assumed that they may likewise remain in the aqueous in living form and, with a later depression of immunity, propagate and produce local inflammation. Their

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From the Eye Service of The Mount Sinai Hospital.

presence in an eye with acute iritis has been bacteriologically proved by culture of the aspirated aqueous. Beeson, Hankey, and Cooper,[5] in 1951, reported evidence of human infection with Leptospira pomona in the United States. They observed that iridocyclitis may occur as a late sequel to such infection. The interval between the initial infection and the ocular inflammation varied, but it was most commonly between 4 and 8 months. Because of this long asymptomatic interval, the etiologic role of the leptospirosis may remain unrecognized. They call attention to the iridocyclitis of horses commonly associated with infection by Leptospira pomona, an organism only recently discovered in cattle in this country. On the basis of the foregoing observations, they carried out serologic tests for leptospirosis on patients with iridocyclitis, utilizing a microscopic slide agglutination test. The following species of live leptospirae were employed as antigens: icterohemorrhagiae, canicola, ballum, grippotyphosa, bataviae, saxkoebing, and pomona. As a screening method, the sera were tested in a dilution of 1:300. One of the sera examined was found to agglutinate L. pomona in high dilution. It was believed that the iridocyclitis was a late sequel to systemic infection contracted by the patient while working in an abattoir seven months previously. Numerous examples of L. pomona infection in human beings have been recognized in other parts of the world, especially Australia and Switzerland.

Oksala and Salminen[6] reported, in 1956, four cases of leptospiral uveitis diagnosed in Finland. They reviewed briefly the ocular manifestations of leptospirosis, such as conjunctivitis and episcleritis, and ephemeral symptoms and signs, such as photophobia, ciliary hyperemia, jaundice, and hemorrhagic phenomena in various parts of the eye. In addition, various pupillary changes occur, such as mydriasis and anisocoria. Ptosis, ocular muscle palsies, papilledema in association with serous meningitis, and, not infrequently, optic neuritis are also ocular complications of the disease. The most important of the ocular complications, however, is uveitis, which can appear as early as the end of the acute febrile stage, but as a rule manifests itself only after an asymptomatic interval of a few weeks' or months' duration. These authors report that in leptospiral uveitis one finds typically a slightly hyperemic iris; finely grained visible aqueous flare; slight, often persistent precipitates, and posterior synechiae easily detachable by mydriatics. In the severer chronic form of the disease, membranate opacities of the vitreous of different patterns are frequently seen, as well as so-called vitreous precipitates. The Finnish authors' diagnosis was based partly on positive titers with the serological leptospiral agglutination lysins test and partly on the clinical picture of the disease. The leptospiral types were as follows: L. bataviae in two patients, L. sejroe in one, and L. poi in one. The cases were found in a group of 66 patients treated for iritis and uveitis. Clinically, the cases primarily resemble the mild form of acute leptospiral uveitis. Three of the patients exhibited roseola formations of the iris in the acute stage of the disease.

Gilbert[7] found as early as 1922, among a group of 200 cases of iritis, 2 associated with Weil's disease, and in Reimer's[8] iritis group of 30 persons, 4 had certain and 2, suspected leptospirosis, but these series did not present any specific clinical picture.

Several different forms have been distinguished by some of the German writers. Doret and Röhm[9] described (1) acute mild iridocyclitis without noticeable vitreous opacities; (2) severe slowly improving iridocyclitis with membranous vitreous opacities characteristic of the disease. Gsell[10] added to these (3) recurring iridocyclitis, which, in his opinion, was rare. According to Pagani,[11] there is (1) a fibrinous form, which is acute and often manifested as early as the febrile stage; it presents the appearance of severe ciliary injection, pronounced visible aqueous flare, blurred iris structure, and posterior synechiae; (2) a serous form, with a later

onset and slighter symptoms but with vitreous precipitates.

During recent years success has been achieved in demonstrating living leptospirae in the fluid of the anterior chamber in association with uveitis after clearing of the acute febrile stage. In Italy, Pagani [11] transferred anterior chamber fluid by pipette into the eyes of guinea pigs, and one of them became infected with leptospirosis. According to Gsell,[10] Cimbal cultivated a strain of L. grippo-typhosa from the aqueous of a patient with chronic uveitis. In a laboratory animal developing uveitis 51 days after onset of infection, Alexander [3] made a culture from the aqueous of the leptospiral strain called L. alexi, which had been handled at the laboratory. Fisher et al.[12] cultivated L. saxkoebing from the aqueous of a patient, but, surprisingly enough, the blood and aqueous of this patient yielded antibodies of L. icterohemorrhagiae. Several workers obtained negative results in cultures from the aqueous, namely, Babel,[13] Reimer,[8] and others. It is noteworthy that Kathe et al.[14] have isolated a leptospiral strain from the eye of a horse with so-called periodical equine iridocyclitis, a common eye disease of horses in Central Europe, caused by leptospirosis.

Leptospiral antibodies were found in the aqueous by Gsell [10] and Doret and Röhm.[9] However, antibodies were not detected in all cases. Austoni [15] expressed the opinion that the cause of the appearance of uveitis is the original absence of the leptospiral antibodies in the aqueous or their quick disappearance from it, after which leptospirae could establish themselves. According to Gsell,[10] it is also possible that leptospirae continue to live in the iris, as they do in the epithelial cells of the renal tubules. In our present state of knowledge, the pathogenesis of leptospiral uveitis can be attributed to the presence of leptospirate and to the allergic and toxic changes produced by them. These findings are further amplified by Fischer, Freytag, and Remsky,[12] who describe the clinical, bacteriological, and serological findings in leptospiral uveitis. They reported uveal infection with L. icterohemorrhagiae one and one-half years after systemic infection and obtained positive agglutination titers from the aqueous. Major Fair,[16] of the United States Army Medical Corps, reported, in 1954, on the importance of leptospirosis as a cause of uveitis among military personnel. Although it is not a common cause of uveitis in the military corps, he feels that it might become so, especially in foreign lands. He points out that the inflammation of the uvea is due to an actual invasion by the leptospiral organism. At Walter Reed Army Hospital, the organism was found by Alexander's [3] group in a case of accidental laboratory infection. In this particular case, a severe unilateral granulomatous iridocyclitis developed five weeks after recovery from the general disease. The serum titer was 1:3,200, after a high of 1:6,400 attained only a week before. An anterior chamber puncture, performed for both therapeutic and diagnostic purposes, revealed the spirochetes upon culture.

Yager, Gochenour, and Wettmore,[17] of the Veterinary Corps of the United States Army, reported a study of periodic ophthalmia in horses, the counterpart of recurrent iridocyclitis in man. A series of 121 samples of equine sera were examined serologically to determine the relationship between recurrent iridocyclitis and the presence of leptospiral agglutinating lysin antibodies. When L. bovis was used as an antigen, antibodies were demonstrated to some degree in the sera of all horses affected with periodic ophthalmia and in fewer than 50% of the sera from normal horses. When an agglutination titer of 1:300 against L. bovis was adopted as significant, 94% of the affected horses had positive titers, in contrast to fewer than 12% from the normal horses.

Evans and Jones [18] reported a case of Weil's disease occurring in an agricultural district of Wales after a rat scratch. They point out that, while much has been published on cases of Weil's disease among British troops in Italy and Normandy in

which infection occurred from bathing pools and rivers, this is the first case where the source of infection could be traced to an actual rat scratch. The other interesting point about this case was that the clinical diagnosis of Weil's disease was made before the method of infection was discovered. They emphasize that in the diagnosis of any condition in which there is a combination of pyrexia, jaundice, and albuminuria, Weil's disease should be borne in mind. This patient had no ocular complications except for early conjunctival hemorrhages.

Moro,[19] from the University of Padova, reviewed the literature on uveitis due to leptospirosis and reported in detail 17 cases. Biological examinations and serologic examination of the aqueous were performed in most of the cases. L. icterohemorrhagiae was the most frequent causative agent. The author observed two main clinical forms: 1. Anterior uveitis, (*a*) serous or serofibrinous, characterized mainly by signs of iritis and iridocyclitis, and (*b*) silent serous cyclitis; 2. Panuveitis.

Anterior uveitis may heal completely in a short time. It may, however, recur and take a chronic form. Extension to the choroid, optic nerve, and retina may follow. Panuveitis may be secondary to anterior uveitis. There is however another form of panuveitis, slow in course, leading to marked changes in the texture of the vitreous body and diminution of vision. One should be careful to distinguish it from tuberculous uveitis.

Austoni and Moro[15] reported on uveitis as a manifestation of oculoinflammatory leptospirosis with special attention to the form of silent serous cyclitis in which there are no subjective symptoms. The uveal signs of leptospirosis are classified as: (1) Acute anterior uveitis, early or late; (2) silent serous cyclitis; (3) slow chronic panuveitis.

Trenkler,[20] in the Czechoslovakian Ophthalmologic Journal, reported two cases of remote ocular complications of L. sejroe. Two cases of iridocyclitis are discussed in this paper. In the first patient, a 46-year-old man, iridocyclitis with vitreous opacities appeared four months after the acute phase of the disease, and both eyes were involved. The course of iridocyclitis was more severe in the later diseased eye and was complicated by hyphema and transitory secondary glaucoma. Serum agglutination of L. sejroe was positive, with a titer of 1:1,600, increased one week later to 1:6,400. Two and one-half months later, the vitreous cleared and visual acuity was regained. In the second case, a 41-year-old man developed purulent iridocyclitis six months after the primary disease. The inflammation followed a malignant course and led to panophthalmitis with seclusion and occlusion of the pupil in spite of treatment. Final visual acuity was finger-counting at 0.5 meter. In both cases the field mouse, Microtus arvales, was the probable source of infection.

Milin and Miletto,[21] of Marseilles, report on ocular complications in leptospirosis. A case of uveitis may sometimes confirm the diagnosis of leptospirosis and may take one of several forms. 1. Posterior uveitis with minimal involvement of the anterior uvea may develop. The symptoms are often so mild that the affliction passes unnoticed and visual acuity is not markedly disturbed. Total recovery is the rule. There may or may not be an optic neuritis in the form of uveopapillitis. 2. Anterior uveitis is much more serious and cannot be clinically masked. There is an insidious onset, frustrating etiology, functional symptoms, such as pain and photophobia, and objective findings, such as ciliary injection, slight miosis of the pupil, impaired pupillary reflex, and irregularity of the pupillary border. In conclusion, he says that the fulminating type of leptospiral iritis is an entity important to remember among the complications of the disease. It should not pass unnoticed and justifies a detailed examination of the eye in patients where the diagnosis may be suspected.

Stergar and Novak[22] present a short survey of the work on Leptospirosis in Yugoslavia. They report their observations

in two cases of leptospiral iridocyclitis caused by L. australis. After analyzing both cases, in which the clinical symptoms are identical with those already described, the authors discussed two so-far-undescribed symptoms, sheathing of the veins and tongue-shaped exudative formations on the optic papilla. Cordier and Algan [23] reported, in 1949, on retinal hemorrhages of leptospiric origin. They had four cases of late iridocyclitis with hyalitis as well as other late complications that are equally classic, such as optic neuritis. It seemed to them worthy of note that, while rare, isolated retinal hemorrhages might also be considered among the possible manifestations of leptospiral infection. Rousseau and Perreau [24] reported, in 1954, on the occurrence of hyalitis on the seventh day of leptospiral infection, whereas classically the pathology of the vitreous and the attainment of uveitis are considered late complications, appearing only exceptionally before four or five weeks. Algan and Vitte [25] write, in 1956, of simultaneous eye and central nervous system infection in the form of a uveomeningitis due to leptospirosis. They report a case in a 30-year-old woman of simultaneous uveitis and meningitis with a lymphocytic response both in the cerebrospinal fluid and in the aqueous humor. The leptospiral origin of the uveitis seemed certain, although they were unable to recover the specific agglutinins from the aqueous humor. They felt that the leptospirosis was a septicemia which secondarily localized itself, with a predilection for the aqueous humor or the cerebrospinal fluid, the two media possessing a certain kinship as to their origin, constitution, function, and absorption. In certain clinical forms the ocular structures are predominantly affected; in others, the central nervous system structures. Lastly, the possibility exists of simultaneous involvement of both.

Report of a Case

The following case of chronic uveitis of the left eye, complicated by secondary glaucoma, came under treatment at the Mount Sinai Hospital during 1956 and attracted considerable attention because of its probable relationship to leptospirosis. The patient was a 29-year-old white man, a resident surgeon, who, three years before the present illness, had been bitten by a rat while working in a research laboratory in Switzerland. Shortly thereafter, he contracted Weil's disease and was treated for it in Switzerland. Within several months he developed a full-blown uveitis in the left eye. He was given atropine eye drops, cortisone eye drops and ointment, cortisone tablets orally, and repository corticotropin injection (ACTH Gel) intramuscularly, and he gradually improved. Two years later he suffered a recurrence of uveitis in the left eye which again responded to medical treatment.

The patient first presented himself in the Eye Clinic of the Mount Sinai Hospital in the fall of 1955, three years after the first onset of the disease, complaining of impaired vision in the left eye. At that time he was observed to have a very slight aqueous flare, which was interpreted to represent a recrudescence of his uveitis. Therefore, the patient was given steroid therapy, both topically and systemically, as well as local mydriatics. During this time, very minimal lens changes were observed in the left eye, but there were no signs of posterior uveitis. The patient was given repository corticotropin injection (ACTH Gel) intramuscularly and, several hours after the injection he began to experience ocular pain, accompanied by headache, nausea, and malaise. The following morning the pain became excruciating, with intense congestion of the eye, lacrimation, and photophobia due to acute secondary glaucoma of the left eye.

Examination showed vision O. D. 20/30, O. S. finger-counting at 1 ft.; tension O. D. 20, O. S. 75. The cornea of the left eye was steamy, the pupil was fixed and widely dilated. The aqueous was turbid with 4+ flare and cells. The anterior chamber was shallow. There was an immature cataract present. The fundus was obscured by the anterior segment changes. Many

vitreous floaters and copious vitreous exudate were present.

The patient was given acetazolamide (Diamox), 500 mg. intravenously, and eserine 0.5% eye drops every 15 minutes for six doses. He was given morphine sulphate, 15 mg. hypodermically, to relieve the intense pain of the acute congestive attack. He then received Metimyd (prednisolone acetate, 0.5%, and sulfacetamide sodium, 10%) eye drops in the left eye every two hours; acetazolamide, 250 mg. by mouth q. i. d.; a preparation of tetracycline HCl and nystatin (Mysteclin), 250 mg. by mouth q. i. d., and, lastly, triple typhoid, 10 million organisms intravenously. Within 24 hours, the intraocular tension of the left eye dropped to 27 mm. On the second hospital day the tension again rose to 53, and so the regimen of acetazolamide intravenously plus eserine eye drops was reinstituted. Again the tension fell to normal within several hours. Over a two-week period of hospitalization the dose of intravenous typhoid was gradually increased to 20 million organisms, then 30 million, 45 million, 50 million, 80 million, and, finally, 120 million. In addition, the patient was given penicillin, 1 million units intravenously daily; chloramphenicol (Chloromycetin), 250 mg. by mouth q. i. d.; acetazolamide, 250 mg. by mouth b. i. d., and Metimyd eye drops in the left eye every two hours. In this way the tension was maintained at normal levels, and the eye became whiter and the cornea, clear. The lens was partially cataractous and possibly slightly swollen, obscuring a good view of the fundus. Vision at this point was finger-counting at 3 ft., and the eye was somewhat exophoric. Some of the vitreous exudate appeared to be clearing. Slit-lamp study was negative for flare and cells. The patient was discharged to the Eye Clinic, continuing to take chloramphenicol, 250 mg. by mouth q. i. d.; acetazolamide, 250 mg. b. i. d., and Metimyd eye drops every two hours.

Before the patient's discharge from the hospital, blood was drawn for leptospiral antibody titers and sent to the National Institutes of Health in Bethesda, Md. The first admission covered the period from May 27 to June 11, 1956. On June 19, the patient presented himself again with a recurrence of severe pain in the left eye for one day. He was again found to have a severe rise in tension of the left eye, with classic signs of acute congestive glaucoma. Examination showed tension O. D. 15, O. S. 61. The cornea of the left eye was slightly edematous; the pupil was moderately dilated; the anterior chamber was shallow, and the iris was somewhat atrophic. The lens was cataractous, and the vitreous contained considerable exudate and numerous floaters. The fundus was obscured. The aqueous was relatively clear at this time. The leptospiral antibody titer was reported by the National Institutes of Health as "moderately positive."

The patient was treated with acetazolamide, 500 mg. intravenously, followed by 250 mg. q. i. d. by mouth; eserine 0.5% and pilocarpine 2% eye drops every 15 minutes for two hours, and then hydrocortisone 0.5% eye drops every two hours in the left eye. On this regimen, the tension again dropped to normal, remaining at about 15 mm. for the next 24 hours. The pupil became miotic, but the anterior chamber of the left eye remained shallower than that of the opposite eye. It was the opinion of the staff that this was the result of a swollen cataractous lens. The patient was then discharged to the Eye Clinic, with instructions to continue taking the acetazolamide, 125 mg. by mouth b. i. d. No further miotics were necessary. Vision in the left eye was finger-counting at three ft. at this time.

During the next two years, the cataract in the left eye became progressively more mature. Vision dwindled to finger-counting at 1 ft. Light projection was perfect. Therefore, on June 2, 1958, a combined extracapsular cataract extraction was performed on the left eye, with a peripheral iridectomy. When the capsule of the cataractous lens was opened and the soft cortical matter was irrigated, no nucleus was found. It is interesting that at age

31 no nucleus was present in the lens, because most of us have been taught that a nucleus develops at about the age of 25 years.

Postoperatively the eye healed well. The fundus could now be observed and was found to be entirely normal. The left exophoria was less prominent. Vision was corrected to 20/20 with a contact lens, which the patient wears with comfort constantly. The left eye, when refracted, accepted $+11.25+0.50\times90$ and obtained 20/20 vision with this lens.

Comment

In appraising the clinical case herein reported in relation to the literature on the subject of leptospiral uveitis, certain observations are noteworthy. In this patient, as in two from the Finnish series,[6] the disease was unilateral. This was true, too, in the laboratory infection reported by Alexander's group[3] at the Walter Reed Army Hospital, in which a severe unilateral granulomatous uveitis developed after a much shorter incubation period. Thus, acute uniocular leptospiral uveitis is possibly not so rare as is sometimes suggested in the earlier literature.[26]

The epidemiology of the leptospiral infection in the case reported is based upon the actual bite of a rat. This situation is undoubtedly the exception rather than the rule, for in most of the documented cases infection came about merely from contact with contaminated murine excreta, with penetration of the spirochete through the abraded skin or mucous surfaces. The instance of infection following a mere scratch of a rat recorded by Evans and Jones[18] lends further credence to the probability of leptospiral infection in the manner described for this patient. With respect to the classification of uveitis proposed by some of the authors, it is felt that this case falls under the heading of anterior uveitis. The absence of ophthalmoscopically visible posterior segment changes probably bespeaks a relatively favorable prognosis, as is borne out by the 20/20 vision obtained after removal of the cataract.

The cases reported by Trenkler[20] from Czechoslovakia are of particular interest in relation to the present patient. Of all the reports reviewed, his is the only one which describes the complication of secondary glaucoma occurring in the course of a severe leptospiral uveitis. In the present case, the secondary rise in tension was the most dramatic event in the clinical course. The recognition of the underlying leptospiral uveitis was the basis for effective management and treatment.

Summary

A case is reported of severe recurrent leptospiral uveitis in one eye which developed several months after the systemic manifestations of Weil's disease. The patient suffered from exacerbations over a period of three years and responded temporarily to medical therapy. The uveitis was then complicated by acute secondary glaucoma plus the formation of a cataract.

A survey is presented of the world literature, with a review of the experience of leading authorities with this rather unusual ocular syndrome. The case at hand is further analyzed against the background of the ophthalmic literature, and certain of the extraordinary features are discussed.

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Mucopolysaccharide Sulfate in the Cornea and Sclera of Rabbits

A Study of the Normal State and After Keratoplasty

ARTHUR NATHANIEL, M.D., and RALPH Z. LEVENE, M.D., New York

As mucopolysaccharides are an important constituent of ground tissue,[1] further knowledge of their properties is of great importance to the understanding of the nature of this tissue. Ocular tissues are rich in mucopolysaccharides, particularly cornea, lens capsule, and vitreous.[1,2]

The turnover of mucopolysaccharides in tissues can be studied with radioactive sulfate tracers. Dohlman and Boström [3] demonstrated that the normal uptake and elimination of the mucopolysaccharide sulfate of the corneal stroma differed markedly from that of the sclera. Dohlman [4] investigated the chemical distribution of radioactive S^{35} among the various sulfate components in different tissues of the rabbit eye. He demonstrated that a large amount of the sulfate in the cornea and sclera occurred as sulfomucopolysaccharide. In vitro studies [5] have demonstrated the uptake by the rabbit cornea of radioactive S^{35} at a rate comparable to rabbit costal cartilage and the subsequent localization of this sulfate in the isolated mucopolysaccharide. The present investigation consists of a further study of the turnover rates of the mucopolysaccharide sulfate in the normal state and after corneal transplantation. The transplanted state was studied in order to determine the fate of this material after keratoplasty.

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From the Department of Ophthalmology, New York University-Bellevue Medical Center.

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Method

The method of Dohlman and Boström [3] was followed with slight modifications. Adult male albino rabbits weighing approximately 3 kg. were used. They were allowed food (Wayne Rabbit Pellets) and water without restriction. Twenty-one rabbits were given intraperitoneal injections with 750μc. of carrier-free S^{35} as sodium sulfate at pH 7. They were divided into seven groups of three each, and each group of animals was killed by intracardial injection of pentobarbital sodium (Nembutal) at various time intervals after the administration of the isotope. The eyes were enucleated, and corneal buttons were obtained by a 10 mm. trephine. The epithelium and endothelium were removed. The scleras were dissected free of muscle stumps, conjunctiva, and fascia, and scleral buttons were similarly obtained by trephine. In order to remove the free inorganic radioactive sulfate, the corneal and scleral buttons were washed in several different baths of one-third saturated sodium sulfate solution with constant agitation for 12 hours. Finally, the specimens were placed between two glass plates to maintain a uniform flat surface during the initial drying with infrared lamp under low heat. The final drying was done in a planchet with the specimens held to the planchet by an albumin fixative. After the final drying, the corneal and scleral buttons appeared as flat discs of uniform diameter. The mean weight ($\pm$ standard error of the mean) of all 50 dried corneal buttons was 14.7 ± 0.43 mg., and the mean weight of the dried scleral buttons was

11.0±0.40 mg. The corneal buttons were thus approximately 30% thicker than the scleral buttons. The efficacy of the washing procedure was tested on several control corneal and scleral buttons that were allowed to imbibe fluid containing radioactive sulfate. The final count after washing was insignificant as compared to the original count. Furthermore, Dohlman and Boström [3] state that less than 5% of the labeled ester sulfate was lost from their specimens after this washing technique. The radioactivity of the buttons was determined by counting in a glass flow counter, and appropriate corrections were made for background and coincidence loss. The density-thickness of these buttons is about 18 mg. per square centimeter, approximately 60% of the value for infinite thickness for S^{35}. Although the count from the 30% corneal excess thickness is considerably minimized by self-absorption, the two tissue button counts are only roughly comparable on a weight basis.

The turnover of radioactive sulfate in homologous grafts was compared with that of autologous grafts by the following method. Twenty-two rabbits were grouped in pairs, and the right corneas of each pair were interchanged as homografts. The left corneas of the animals were removed and replaced as autografts. Ten millimeter keratoplasties were performed under chlorpromazine hydrochloride (Thorazine) and pentobarbital sodium (Nembutal) anesthesia, with use of edge-to-edge (000000) nonabsorbable (silk) surgical sutures. After the operation, chlortetracycline hydrochloride (Aureomycin) and atropine ointments were instilled daily until the animals were killed.

These animals were divided into two groups. One group received 500μc. of radioactive sulfate one week after keratoplasty, while the second group received a similar dose two weeks after keratoplasty. In both groups, the animals were killed at 6-, 24-, and 48-hour intervals after the administration of the isotope. Before killing the animal, the anterior chamber fluid was removed by tuberculin syringe with a 27-gauge needle. After the animal was killed, the eyes were enucleated and corneal and scleral buttons were obtained with a 10 mm. trephine. The specimens were washed, dried, and counted in a flow counter as described above. The mean weights of all the dried tissue buttons from autografts and homografts did not differ significantly from the normal mean values given above. The radioactivity of the aqueous diluted 1:10,000 was determined as counts per minute per milliliter.

TABLE 1.—*Turnover of Mucopolysaccharide in the Rabbit Cornea and Sclera* *

	Hr. After Injection						
Tissue	3	6	12	24	48	100	200
	650	1,188	2,200	2,967	2,200	1,990	1,264
	691	1,230	2,450	2,972	2,320	1,970	1,425
	641	1,238	2,200	2,958	2,250	1,860	1,265
Cornea	652	1,247	2,214	2,955	2,215	1,960	1,400
	702	1,283	2,248	2,943	2,215	1,888	1,310
	702	1,277	2,248	2,940	2,300	1,990	1,496
Mean	688	1,243	2,260	2,956	2,250	1,943	1,360
	361	577	1,780	963	835	571	347
	370	587	1,775	897	700	625	300
	360	596	1,625	1,004	840	570	348
Sclera	360	611	1,775	980	750	625	410
	348	686	1,770	972	720	600	320
	343	633	1,775	984	835	615	375
Mean	357	615	1,750	966	780	601	350

* Expressed as counts per minute per corneal or scleral button.

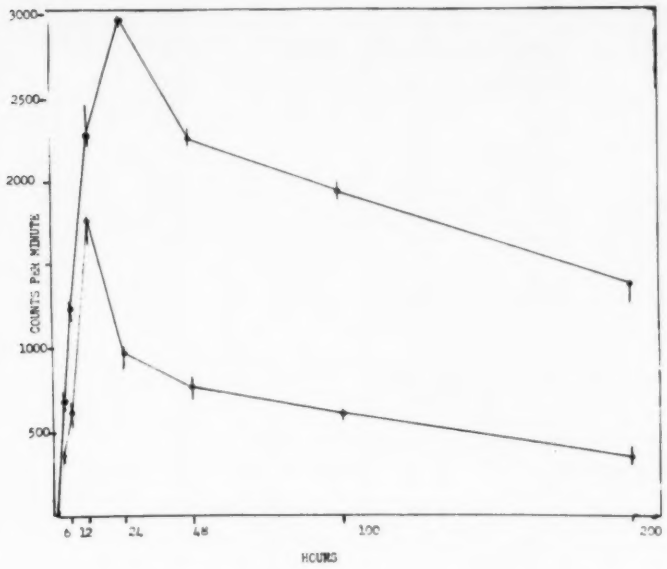

Fig. 1.—Turnover of mucopolysaccharide sulfate in the rabbit cornea (upper curve) and sclera (lower curve). Each point represents the mean of the values from six eyes, and the vertical bar indicates the range.

Results

The results on the S^{35} sulfate turnover in normal corneal and scleral tissue buttons are presented in Table 1 and are graphed of S^{35} sulfate by the cornea differed markedly from that of the sclera. The scleral curve reached its maximum of 1,670 counts per minute after 12 hours, fell rapidly during the next 12 hours, and then declined more slowly for the remainder of the experiment. From 24 hours to 200 hours the biological half-life of the sclera was five days. The corneal curve showed a higher peak of 2,956 counts per minute at 24 hours, fell rapidly for the next 24 hours, and subsequently declined more slowly to

TABLE 2.—*Sulfate Uptake in Homograft and Autograft Tissues After Seven Days* *

	6 Hr.			24 Hr.			48 Hr.		
Tissue	Homograft	Autograft	% Difference †	Homograft	Autograft	% Difference	Homo-graft	Auto-graft	% Difference
	1,099	746	+32	1,041	768	+26	941	751	+20
	1,528	892	+41	1,750	1,430	+18	975	784	+19
Cornea	1,849	1,811	+ 2	1,379	743	+46	987	699	+22
	1,633	504	+69	1,170	1,076	+ 8	1,309	786	+39
Mean			+36			+24			+25
				366	197	+46	213	144	+32
	134	104	+22	653	371	+43	289	180	+37
Sclera	328	247	+24	298	180	+39	340	189	+44
				504	299	+60			
Mean			+23			+47			+37
Aqueous	5,754	3,172	+44	1,255	899	+28	2,130	1,440	+32
humor ‡	6,144	3,376	+45	2,497	1,067	+57	2,890	1,800	+37
	5,758	3,078	+46				3,400	1,890	+44
Mean			+45			+42			+37

* Expressed as counts per minute for trephined corneal and scleral buttons.

† Per cent difference expressed as $\frac{\text{cpm homotissue} - \text{cpm autotissue}}{\text{cpm homotissue}} \times 100$.

‡ Expressed as counts per minute for 1 cc. of aqueous humor diluted 1:10,000.

TABLE 3.—*Sulfate Uptake in Homograft and Autograft Eyes Fourteen Days After Keratoplasty*

Tissue	6 Hr.			24 Hr.		
	Homograft	Autograft	% Difference †	Homograft	Autograft	% Difference
Cornea	1,511	774	+48	1,644	1,524	+ 7
	1,471	736	+49	1,622	1,247	+23
	1,625	641	+60	1,303	874	+32
	1,817	466	+74			
Mean			+57			+20
Sclera	616	323	+47	261	192	+26
	336	183	+45	352	180	+48
	556	131	+76			
	351	169	+51			
Mean			+54			+37
Aqueous humor ‡	6,543	4,233	+35	739	467	+36
	3,868	2,692	+30	727	321	+55
	5,947	4,284	+27	971	812	+16
Mean			+31			+35

* Expressed as counts per minute for trephined corneal and scleral buttons.

† Per cent difference expressed as $\frac{\text{cpm homotissue} - \text{cpm autotissue}}{\text{cpm homotissue}} \times 100$.

‡ Expressed as counts per minute for 1 cc. of aqueous humor diluted 1:10,000.

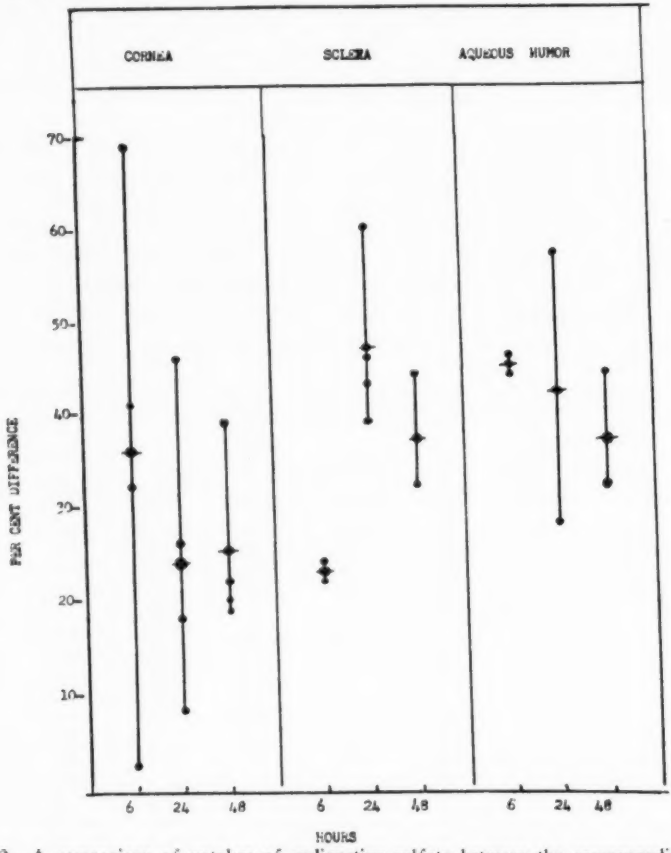

Fig. 2.—A comparison of uptakes of radioactive sulfate between the corresponding tissues of the two eyes of the same animal seven days after corneal homotransplantation in one eye and corneal autotransplantation in the other eye. The mean of each group is indicated by a large winged dot. Each point was obtained by calculating the per cent difference of counts per minute by $\frac{\text{cpm homotissue} - \text{cpm autotissue}}{\text{cpm homotissue}} \times 100$.

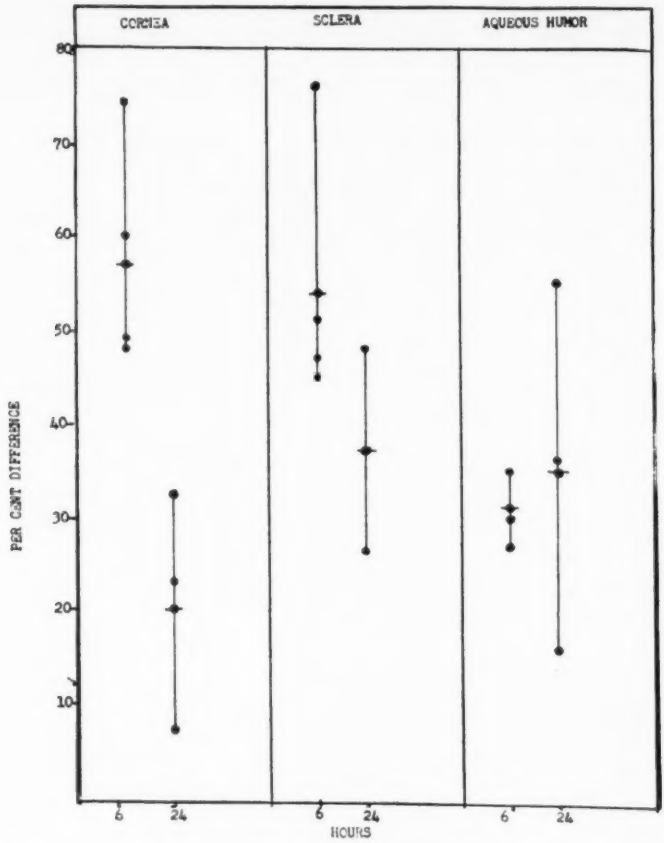

Fig. 3.—A comparison of uptakes of radioactive sulfate between the corresponding tissue of the two eyes of the same animal 14 days after corneal homotransplantation in one eye and corneal autotransplantation in the other eye. The mean of each group is indicated by a large winged dot. Each point was obtained by calculating the per cent difference of counts per minute by $\frac{\text{cpm homotissue} - \text{cpm autotissue}}{\text{cpm homotissue}} \times 100$.

the end of the experiment. From 18 to 200 hours the approximate biological half-life of the cornea was eight days. It should be noted that on linear graph paper the ratio of the half-lives is not equal to the ratio of the slopes of the curves.

The results obtained from the one- and two-week grafts of corneal-transplanted animals are presented in Tables 2 and 3 and are graphed in Figures 2 and 3. They are essentially similar. In general, the radioactivity of all tissues associated with homografts was greater than that of corresponding tissues of the autograft.

Comment

According to Dohlman and Boström [3] the radioactivity of the washed corneal and scleral buttons is mainly due to mucopolysaccharide sulfate. The general shapes of the rabbit turnover curves in this investigation are similar to their curves for the rat. However, the observed biological half-life for the rabbit sclera, five days, is shorter than their result of 10 days in the rat. Again, the observed eight-day biological half-life of the rabbit cornea is shorter than the 32-day result noted by Dohlman for the rabbit.[4] In both cases the corneal turnover

was slower than that of the sclera. The difference in the corneal and scleral turnover curves may be due to a difference in the delivery rates of radioactive sulfate to the two tissues or to a difference in the concentrations or turnover rates of the exchangeable mucopolysaccharide sulfate of the cornea and sclera. It must be realized that the sulfate turnover rate may not represent the turnover rate of the entire mucopolysaccharide molecule. It is probable that the different components of this complex substance metabolize at different rates.

The existence of a mucopolysaccharide sulfate turnover rate in all grafts indicates that this component of the grafted cornea was slowly replaced by the donor tissue. The problem of determining the fate of transplanted tissue should be approached not only in terms of qualitative replacement of the graft by the donor but also in terms of quantitative alterations in tissue replacement rates. The autograft was used as a base line for comparison in order to minimize the effects of surgical trauma. It is interesting to note that the difference in turnover rates was not limited to the transplanted corneas themselves but was evident in the adjacent aqueous humor and sclera.

The difference in radioactivity between the tissues associated with the homograft and those of the autograft can be related to the factors mentioned above. The delivery of the radioactive sulfate to the homograft may be more rapid than that to the autograft due to a greater vascularity or a greater permeability of boundary membranes. Again, the difference may be due to alterations in the concentrations or turnover rates of the exchangeable mucopolysaccharide sulfate itself in the newly grafted states. The enhanced radioactivity of the homograft as compared to that of an autograft is consonant with an immunologic response to the former tissue.

Summary

The uptake and elimination of the radioactive sulfate in the corneal and scleral tissue buttons of normal adult rabbits was followed for 200 hours. The uptake of cornea differed markedly from that of the sclera. The scleral curve reached its maximum at 12 hours and after 24 hours fell steadily, with a biological half-life of five days. At 24 hours the corneal curve showed a peak of nearly twice that of sclera and after 48 hours fell steadily, with a half-life of eight days.

The turnover of radioactive sulfate in homologous grafts was compared with that of autologous grafts. The radioactivity of all the tissues associated with the homografts was greater than that of the corresponding tissues of the autografts. The enhanced radioactivity of the homograft is consonant with an immunologic response.

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Electron Microscopy of Ocular Tissue*

L. K. GARRON, M.D.; M. J. HOGAN, M.D.; W. K. McEWEN, Ph.D.; M. L. FEENEY, A.B., and JOAN ESPERSON, Medical Illustrator, San Francisco

The electron microscope reveals structures not otherwise discernible and may thus contribute to our knowledge of anatomic detail and physiologic process. This exhibit presents the results of a preliminary survey of portions of four tissues of the eye: the trabeculae, choroid, iris, and cornea.

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* Shown as a scientific exhibit of the Section on Ophthalmology at the 107th Annual Meeting of the American Medical Association, San Francisco, June 23-27, 1958.

Trabeculae

It is probable that the trabecular meshwork is the site of changes responsible for open-angle glaucoma. Figure 1 shows a montage of that portion of the trabecular meshwork adjacent to Schlemm's canal. The inner wall of Schlemm's canal is lined with endothelial cells, many of which appear to have giant cytoplasmic vacuoles. The adjacent meshwork is composed of trabecular bands, loosely arranged to form intercom-

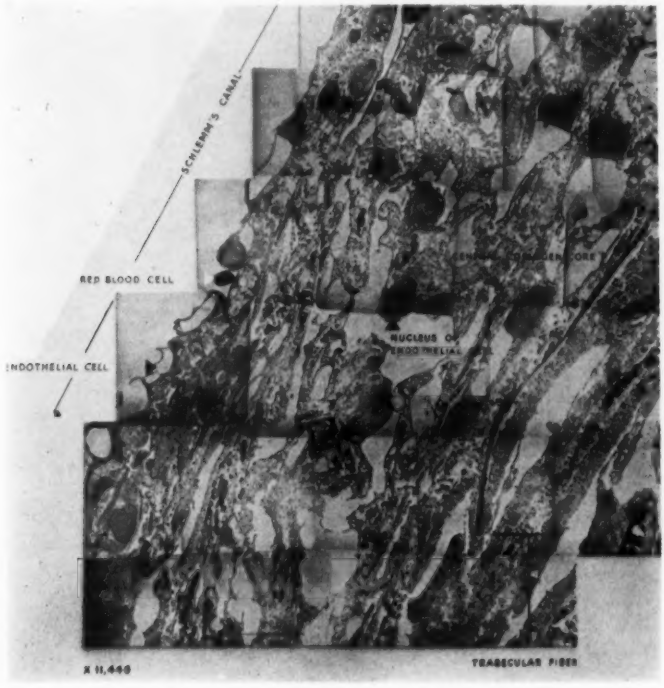

Figure 1

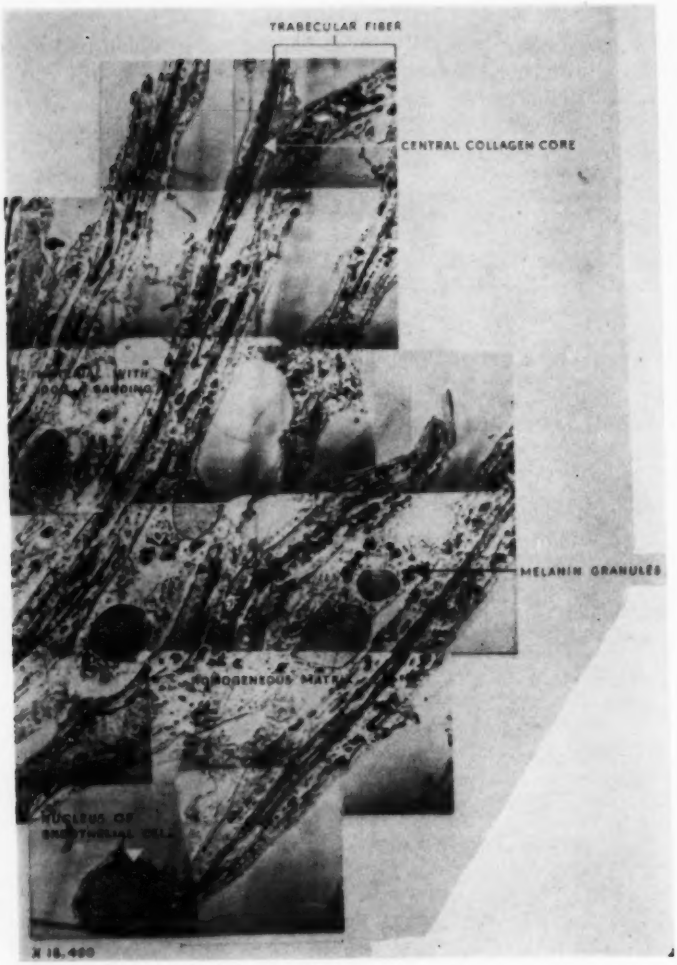
TRABECULAR FIBER
CENTRAL COLLAGEN CORE
MELANIN GRANULES
X 18,400

Figure 2

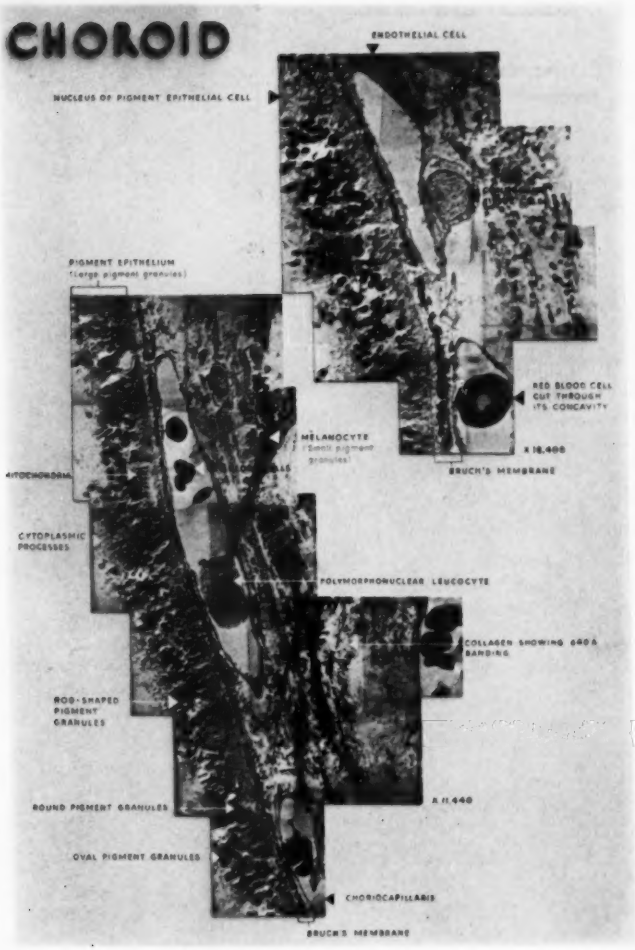
CHOROID
ENDOTHELIAL CELL
NUCLEUS OF PIGMENT EPITHELIAL CELL
PIGMENT EPITHELIUM
(large pigment granules)
RED BLOOD CELL CUT THROUGH ITS CONCAVITY
MELANOCYTE
(Small pigment granules)
x 18,400
BRUCH'S MEMBRANE
MITOCHONDRIA
CYTOPLASMIC PROCESSES
POLYMORPHONUCLEAR LEUCOCYTE
COLLAGEN SHOWING 640 Å BANDING
ROD-SHAPED PIGMENT GRANULES
x 11,440
ROUND PIGMENT GRANULES
OVAL PIGMENT GRANULES
CHORIOCAPILLARIS
BRUCH'S MEMBRANE

Figure 3

municating spaces. The endothelial cells covering the bands show cytoplasmic degenerative changes, probably as a result of poor fixation.[1]

In Figure 2, the trabecular meshwork has been cut to expose longitudinal sections of the central collagen core. The exposure of the core for a considerable portion of its length suggests that the eye was cut in the tilted frontal plane, as described by Ashton.[2]

Choroid

Figure 3 shows a montage of the inner portion of the choroid and of the adjacent retinal pigment epithelium. This latter structure contains pigment granules which are predominantly round and oval, occasionally rod-shaped, and much larger (two to three times) than the pigment granules of the melanocytes in the choroid.

Bruch's membrane appears to be a three-layered structure, but a complete correlation with the accepted two-layered histologic picture has not yet been completed.

Some of the cellular components of the choroidal stroma are illustrated in Figure 4.

Iris

The large montage in Figure 5 shows a diagonal section of the pigment epithelium of the iris and adjacent muscle layer. In this montage, the fibers of the muscle cells are in cross section; in the small montage at the top, they are in longitudinal section.

The left panel shows some of the components of the iris stroma, i. e., a thick-walled capillary, two pigment-containing cells, and a myelinated nerve with its Schwann cell.

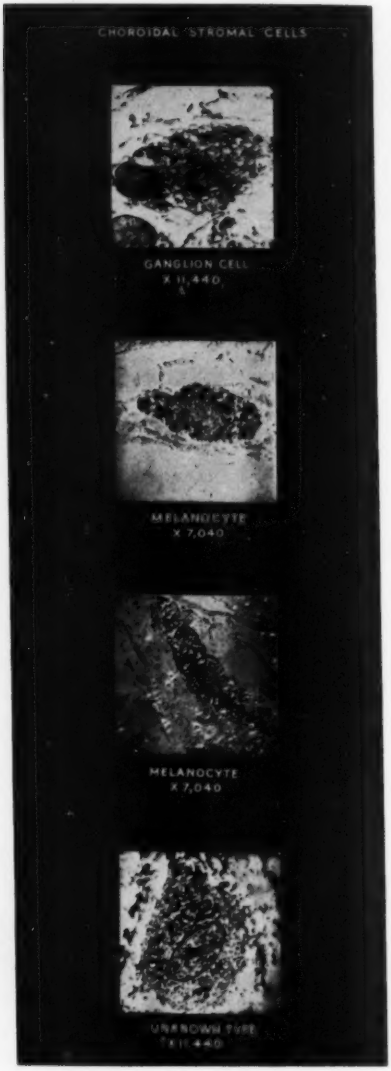

Figure 4

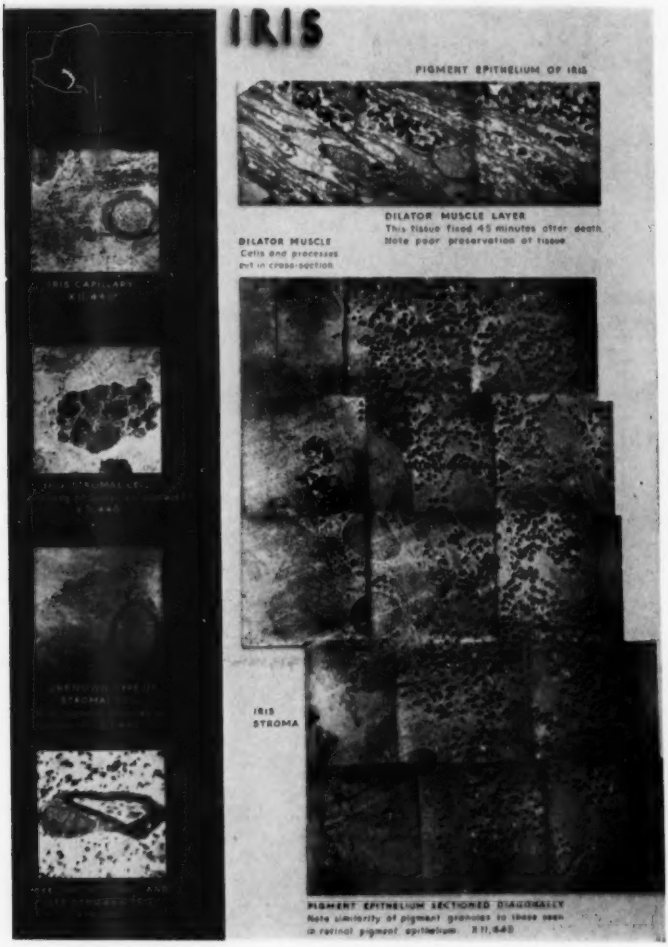
IRIS
PIGMENT EPITHELIUM OF IRIS
DILATOR MUSCLE LAYER
This tissue fixed 45 minutes after death.
Note poor preservation of tissue
DILATOR MUSCLE
Cells and processes
cut in cross-section
IRIS
STROMA
PIGMENT EPITHELIUM SECTIONED DIAGONALLY
Note similarity of pigment granules to those seen
in retinal pigment epithelium. X 11,640

Figure 5

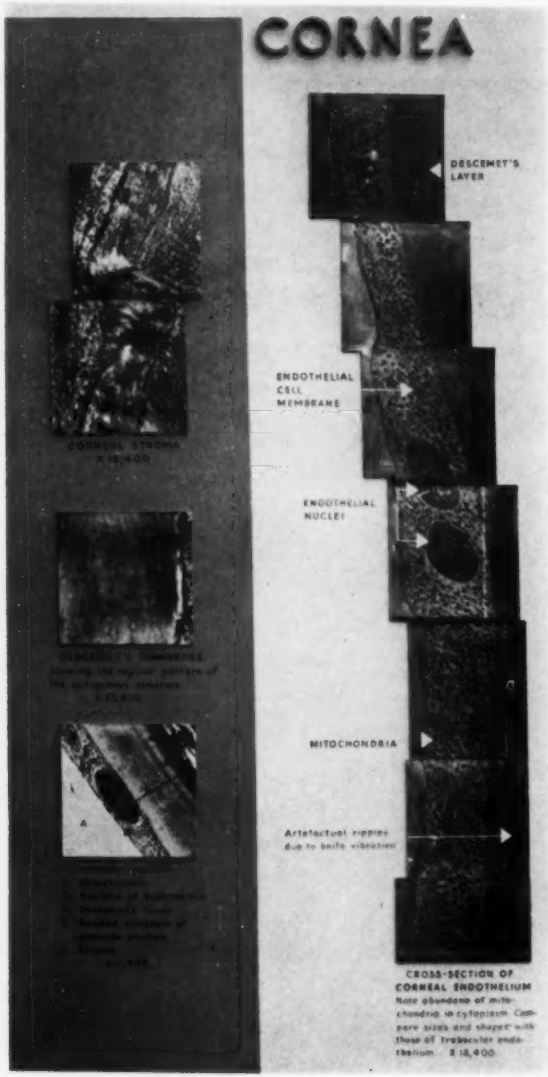
CORNEA
DESCEMET'S LAYER
ENDOTHELIAL CELL MEMBRANE
ENDOTHELIAL NUCLEI
MITOCHONDRIA
Artefactual ripples due to knife vibration
CROSS-SECTION OF CORNEAL ENDOTHELIUM
Note abundance of mitochondria in cytoplasm. Compare sizes and shapes with those of trabecular endothelium. X 18,400

Figure 6

Cornea

Figure 6 shows a montage of the corneal endothelium with a portion of Descemet's membrane. The endothelial cells contain many more mitochondria than are found in the endothelial cells of the trabeculae.

University of California, Francis I. Proctor Foundation (22).

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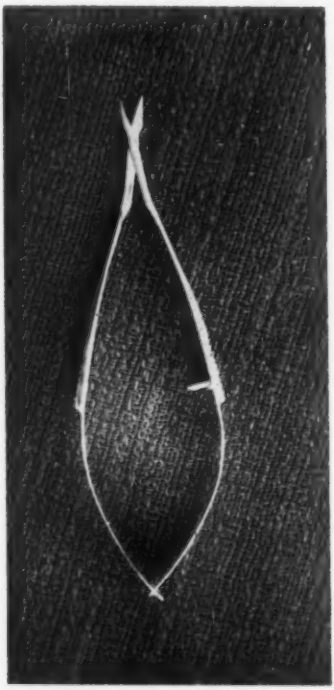
Vannas Scissors for Removing Corneoscleral Sutures

CHARLES T. MEACHAM, M.D., Stamford, Conn.

This article is written for those of us who prefer to use nonabsorbable surgical (silk) sutures instead of absorbable surgical (gut) sutures.

The difficulty and danger which is sometimes encountered in removing corneoscleral sutures led me to seek a safer and easier method. First, the use of forceps was eliminated in favor of using scissors alone. For this purpose very fine-bladed cuticle (manicuring) scissors were found satisfactory except in the case of a very apprehensive and uncooperative patient. Next was the attempt to untie the suture knot. This was found easy to do with jeweler's fine pointed forceps except in the case of very tight or deeply buried knots.

However, noting the ease with which the sutures could be grasped with these forceps, I conceived the idea of scissors which would give the same feel and ease of handling—delicate narrow-bladed ones with spring action handle. Vannas (straight) capsulotomy scissors met those requirements (Figure).



The method used by me is to stand in front of and a little to the right of the patient, who is tilted back somewhat (I use a Ritter chair) and looking down. Tetracaine drops are instilled, and while the upper lid is held elevated with the left thumb, it is usually easy to pass one blade through the suture loop and quickly sever it. In so doing, the scissors blades are held barely open and are always pointed in an upward direction so as to avoid getting caught or tangled in the suture in case of unexpected movements. If the eye suddenly rolls up, the suture usually glides off the blades, thus avoiding pain and danger of opening the incision.

The advantages are safety, speed, and more comfort to the patient, since there is little likelihood of pulling on the suture to cause pain.

Vannas scissors are so easy to handle that one can use them with skill on the very first try. In my experience they make all others seem awkward.

Submitted for publication Nov. 13, 1958.

65 South St.

Registry of Interesting Cases

It is the purpose of this section to record cases on the basis of interest only. No complete review of the literature is attempted, and no claim for priority is implied except when specifically stated. Publication of case reports is subject to the concurrence of the Editorial Board on the interesting aspects of the case. It is requested that the reports submitted be as brief as is consistent with inclusion of the pertinent facts, bear a title that is as specific as possible, be prefaced by a paragraph that states why the author feels the case is of interest, and be accompanied with photographs whenever possible.

Absence of Ocular Signs with Cerebellar Ablation in an Infant

It is generally well known that involvements of the cerebellum may account for a variety of signs. These are ataxia and hypotonia homolateral to the side of the lesion, nystagmus, skew deviation of the eyes, and change in the position of the head. It is not so well known that signs of acute involvement of the cerebellum tend to disappear and that failure of cerebellar development may be asymptomatic. Recently a child whose cerebellum was removed has come to our attention, through Dr. Frank Otenasek. Probably the cerebellum had never functioned. The case seems worthy of a brief report.

Report of Case

A white girl 6 weeks old had an orange-sized mass in the occipital region. The skin over the mass was thin. Transillumination suggested that the abnormality was a meningocele. X-rays showed a huge midline defect in the occipital bone extending into the foramen magnum. The cranial vault anteriorly appeared flattened and deformed. Cerebellar signs were not present. The child was subjected to operation one week after admission to the hospital.

The operation note is as follows: "This child was born with a mass, the size of an orange, protruding from the occipital region. It transilluminated so readily that we thought it was a pure meningocele. The sac was opened, and we entered a huge cyst which contained clear fluid. The wall of the cyst was lined with cerebellar tissue, two or three mm. thick. At the base there was a nubbin of unidentifiable brain tissue, about the size of a plum. Two masses of choroid plexus could be seen each projecting from an opening on the side. At first we were disinclined to do anything but then felt that, since the tissue was probably nonfunctional, resection should be tried. The base was therefore cauterized and cut around. The choroid plexus remnants were removed. There was an opening in the base of the skull continuous with the foramen magnum, about 1.5 cm. in diameter. Excess skin was cut away. Thickened subcutaneous tissue was imbricated over the opening. The wound was closed with silk in layers. It would appear that practically the entire cerebellum was removed. The structures in the fourth ventricle were unidentifiable. The baby had no respiratory difficulty during the resection . . ."

When the child was 2 years of age the eyes were seen to be normal externally except for weakness of abduction of the left eye. The child obviously saw toys held in front of it but rarely reached for them. The right optic disc was paler than the left,

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Summer fellow in ophthalmology, Fight for Sight Fellowship of the National Council to Combat Blindness, Inc., New York (Dr. Wania).

which seemed normal. There was no nystagmus, and there were no abnormal movements of the head or body. The child was able to sit up without support and held her head normally. She could walk in a stroller. The child was unable to talk except for saying simple words, such as "mama." There was no evidence of spasticity or ataxia. However, the strength of all four extremities was below normal.

Comment

This case report is of interest in that the absence of cerebellar signs in this patient conforms generally to present knowledge concerning cerebellar ablations in experimental animals. This work has been reviewed by Bard, also by Henneman, and more recently by Walsh. From the standpoint of clinical diagnosis, important facts are stated by these physiologists. Some of these are as follows: 1. Abnormal functioning of the body after removal of the cerebellum is dependent upon abnormal functioning of the remainder of the central nervous system. 2. After removal of the cerebellum, signs present during the acute stage tend to disappear. 3. Nystagmus does not develop if the floor of the fourth ventricle is not injured during the removal of the cerebellum.

Seemingly the cerebellum in this child had not functioned during the first weeks of life. Two years after operation there was no recognizable sign of a cerebellar involvement, unless the hypotonia could be so considered.

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J. H. WANIA, M.B.B.S.
F. B. WALSH, M.D.
14 W. Mt. Vernon Pl.
Baltimore 1

Ocular Sarcoidosis

RAY H. NIELSEN, M.D., North Hollywood, Calif.

To familiarize ourselves with the clinical entity known as sarcoidosis, some of the general features of the disease will be taken up before the ocular manifestations are considered.

History

In retrospect, probably the first case of sarcoid was recorded by Jonathan Hutchinson in 1869, under the name of Mortimer's malady. Then in 1889, Besnier described another case but thought it was different from the case of Hutchinson, so he called it lupus pernio. Boeck, in 1899, described a patient with skin nodules and did the first histologic examination of a lesion. He thought that histologically the lesion resembled a sarcoma and therefore called the lesion sarcoid. He recognized that Mortimer's malady, described by Hutchinson, was of a similar character. In 1902, Kienboch first described the cyst-like changes of the small bones in this disease. Heerfordt, in 1909, noted uveitis associated with enlargement of the parotid gland, but this was not recognized as a manifestation of sarcoidosis until 1936. Finally, in 1914, Schaumann showed it to be a widespread disease entity and demonstrated the histological relationship between the skin and the bone lesions. In 1924, he related all the characteristics of sarcoid into one disease syndrome, and the syndrome has been studied extensively since.

Incidence

Sarcoidosis was considered to be comparatively rare until attention was focused on it by studies between 1936 and 1938. Sarcoidosis proves now to be common in this country as well as in Europe. Freiman estimated that well over 1,000 cases had been reported by 1948, and some of the largest series have been reported since then, such as the 300 cases reported by Ricker and Clark and the 150 cases reported by Gravesen.

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Age, Race, and Sex Incidence

Reports from different parts of the country vary, but the disease appears to occur most commonly in the third and fourth decades, to be commoner in Negroes than in whites, and to be commoner in women than in men.

Distribution of the Lesions

One of the outstanding features of sarcoidosis is the wide and spotty distribution of the lesions. Almost any tissue may be affected. Starting with the tissue most frequently involved and then decreasing to the tissue least frequently involved, the order is lung, lymph nodes, eyes, skin, spleen, liver, nervous system, bones, heart, parotid glands, nose or sinuses, and the kidneys.

Etiology

The cause of sarcoidosis is at present unknown. The most popular concept in the past and the hardest to disprove is that sarcoidosis is a variety of tuberculosis. There are still some who champion a tuberculous etiology, and the reasons they give are as follows:

1. The strong histological resemblance between the involved tissues of the two diseases.

2. The high incidence of clinical tuberculosis in sarcoid patients. Longcope states

that the incidence of tuberculosis in autopsied cases ranges from about 15% to 25%.

3. Instances in which sarcoidosis has apparently changed to tuberculosis.

4. The occasional finding of tubercle bacilli in sarcoid lesions.

5. Patients with sarcoidosis cannot be sensitized to tuberculin by means of a B. C. G. vaccine, which is supposed to show that these patients have a partial immunity to tuberculosis by contact with tubercle bacilli.

Those who feel that sarcoidosis does not have a tuberculous etiology support their contention with the following reasons:

1. True caseation does not occur in sarcoid, while it is very common in tuberculosis.

2. Huge giant cells with curious inclusion bodies are common in sarcoid and are exceedingly rare in tuberculosis.

3. Involvement of the myocardium is not very unusual in sarcoid but is rarely seen in tuberculosis. On the other hand, involvement of serous surfaces and the adrenal gland is common in tuberculosis, but they are rarely involved in sarcoid.

4. Repeated cultures of sarcoid tissue rarely grow any tubercle bacilli.

5. Sarcoid patients show an anergy or lack of response to high doses of tuberculin. This refractory state is not only commoner in patients with sarcoidosis than in the general population, but it is frequently exaggerated to an unusual degree.

6. A positive complement-fixation test for tuberculosis was obtained in only 27.3% of sarcoid patients, and it was found that this was almost exactly the figure which could be accounted for by old or latent tuberculosis in these patients.

7. A strong argument against a tuberculous etiology is the use of the hemagglutination reaction of Middlebrook and Dubos to detect antibodies to some fraction of the tubercle bacilli present in the serum of patients. After a great deal of work comparing tuberculous patients with controls, they concluded that only reactions in titers of 1:8 or above are indicative of tuberculosis. They tested eight cases of sarcoidosis, and in these cases there were no positive tests in titers as high as 1:8. As a matter of fact, in two patients the titer was 1:2, which was the average control level, and the serum from the other six sarcoid patients gave entirely negative reactions.

According to Friedman, most authors now believe that a specific virus or a nonspecific reaction of the body tissues to a number of agents is the cause of sarcoidosis. However, the only accurate statement that can be made with our present knowledge is that the cause of sarcoidosis is unknown.

Pathology

According to Longcope, the microscopic appearance of the lesions of sarcoid reproduces itself over and over with a regularity which has been aptly termed "monotonous." The fundamental microscopic appearance is the same regardless of where the lesion occurs in the body. In its most characteristic form it consists of densely packed masses of epithelioid cells, often associated with many giant cells of the Langhans type. Curious burr-like basophilic bodies, called Schaumann bodies, are occasionally seen in the cytoplasm of the giant cells. These bodies are not specifically pathognomonic of sarcoidosis, since they occur, though more rarely, in some other granulomatous lesions. The sarcoid nodules have little tendency to caseate, although occasionally the central portion of the lesions undergo a form of granular necrosis. This is usually readily distinguishable from true caseation. There is much less tissue destruction with sarcoid nodules than with other granulomatous lesions, and healing may take place with negligible scar formation. If such resolution does not occur, the lesions heal by the process of sclerosis, in which the granuloma is gradually transformed into a relatively acellular mass of hyaline material, and this in turn is followed by a dense fibrosis. Although the epithelioid cell and the giant cell are the most prominent histologic elements in the sarcoid granuloma, other cellular elements

may be seen as well. Lymphocytes may be seen in small numbers usually surrounding the epithelioid cell nodule, and they are very scanty compared to those seen in other granulomas. Plasma cells are occasionally observed. Neutrophils are extremely rare. Eosinophils are frequently found to be elevated in the circulating blood in sarcoidosis but are infrequent in the lesions themselves, and if many are present it casts doubt on the diagnosis of sarcoid as the cause of the granuloma.

General Clinical Features

In its multiplicity of signs and symptoms, in its irregular progression with regressions and exacerbations, and in its long periods of hidden latency, sarcoidosis can be compared to syphilis and tuberculosis, while in its distribution through the body it can be likened to Hodgkin's disease. In one respect, however, it differs entirely from these serious infections and granulomata, for the disease is remarkably benign in its nature and a great many patients seem to recover completely from it. The onset is generally insidious, and in some cases it is discovered in a person who enjoys perfect health. Many patients, however, experience a great variety of vague or indefinite symptoms preceding by weeks or months the physical evidence of illness. As was pointed out earlier in discussing the distribution of lesions, sarcoidosis is a systemic disease with a widespread distribution of the lesions. The effects of the disease vary with the sites of the deposits, the most serious symptoms occurring when the eyes or lungs are involved. It is important that an early diagnosis be made, since the prognosis is greatly improved by early treatment.

The laboratory findings are nonspecific and are not of great help in arriving at a positive diagnosis. In a small percentage of cases due to bone involvement, there may be rarefaction of the medulla of the long bones, particularly the phalanges. In the great majority of cases, however, the x-rays are normal. Some of the other nonspecific changes which may occur include an increased sedimentation rate; a disturbance in the albumin-globulin ratio in the plasma, with an elevation of the globulin fraction; a mild rise in blood calcium, and, as has been mentioned previously, a remarkable anergy to tuberculin. Some patients are nonreactive to enormous doses of tuberculin, even up to 3 or 10 mg., while a patient with a tuberculosis may show a marked reaction to 0.001 mg. of tuberculin. The test which probably is of most value is the Kveim test. This consists of the intradermal injection of a saline suspension prepared from sarcoid tissue. The most potent antigen comes from sarcoid lymph nodes. In a patient with active sarcoidosis a dusky-red nodule develops at the site of the injection during the next three to four weeks. The nodule is then excised and examined histologically and in sarcoid patients reveals characteristic sarcoid tissue. The reaction is negative in normals or in patients with tuberculosis but is positive in cases of active sarcoidosis and has been found to be positive in 80% of cases of ocular sarcoid. It has been shown that the same reaction can be evoked in the skin of sarcoid patients by injecting emulsions of normal human spleen, tissue from a patient with leukemia cutis, B. C. G. vaccine, and living and heat-killed tubercle bacilli. In this sense, the test is not specific, but, as positive tests do not occur in normals or patients with tuberculosis, it shows the altered reactivity of the skin of sarcoid patients and therefore is of value. Thus, in the absence of easily accessible lesions for biopsy, the Kveim is a simple, safe, fairly specific outpatient technique for providing histological evidence of active sarcoidosis.

Ocular Manifestations

The incidence of ocular sarcoidosis in cases of generalized sarcoidosis varies considerably in the statistics reported by different observers, and it ranges from the small figure of 8.7% to the unusually large estimate of 64%. In most series the incidence is found to be around 30% to 40%.

Almost all the structures in and around the eye may become involved.

The most frequent and important of all ocular sarcoid lesions is a uveitis which occurs in 55% of cases of ocular sarcoid. The commonest form of uveitis is a granulomatous type of iritis which is usually painless, bilateral, and accompanied by iris nodules. The nodules are usually discrete and distributed irregularly over the surface of the iris. They are usually somewhat larger and pinker than the iris nodules of tuberculosis. In the somewhat smaller iris tubercles in tuberculosis, the capillaries tend to surround the tubercle and fan out into the adjacent iris. In sarcoidosis the capillaries tend to form a network through and over the nodules. There is usually a minimum of ciliary inflammation, and the keratic precipitates are of the mutton-fat type. Occasionally koeppe nodules are found both in the torpid and in the acute phases. In a small number of cases the iritis assumes the picture of a heavy plastic iritis with inflammatory exudates somewhat veiling the details in the iris. The iris nodules may absorb completely or heal with hyalinization and fibrosis, leaving permanent white nodules on the iris surface or at the pupillary border. Sarcoid nodules of the choroid and retina are rare. They usually appear as deep nodules with little or no surrounding edema or inflammation. Occasionally the nodules have a millet-seed appearance and have a preretinal distribution. Rarely there is a periphlebitis of the retina.

There are two uveitis syndromes which are now thought to be due to sarcoidosis. The first of these is Mikulicz's syndrome, which is a painless, bilateral, chronic symmetrical enlargement of the lacrimal and salivary glands and is often associated with a bilateral nodular uveitis. Woods states that Mikulicz's syndrome with uveitis has a sarcoid etiology, but this is probably not true. As Duke-Elder states, these cases do not constitute a single pathological entity and several entities must be taken into consideration in the differential diagnosis, such as the lymphomas, sarcoidosis, tuberculosis, syphilis, mumps, uveoparotid fever, encephalitis, and Graves' disease. When Mikulicz's syndrome is due to sarcoidosis it is thought to be a variant of uveoparotid fever, which is a definite sarcoid entity and is really a striking outward manifestation of widely disseminated and active sarcoidosis. Uveoparotid fever, or Heerfordt's disease, is a mildly febrile enlargement of especially the parotid and submaxillary glands. There is frequently an associated facial palsy, and the disease usually begins with malaise, lassitude, gastrointestinal symptoms, ill-defined cerebral symptoms, and often a skin eruption resembling erythema nodosum. The uveitis and glandular enlargement develop early and are the salient features of the disease. The prognosis for life is good, but the occular morbidity is high.

Ocular manisfestations of sarcoidosis other than uveitis are rare. The skin of the eyelids may become involved, like the skin elsewhere over the body, with the usual small millet-seed-like nodules of sarcoid in about 8% of cases. Also in about 8% of cases the lacrimal gland only is involved without giving the picture of Mikulicz's syndrome. This lacrimal gland involvement is painless, firm, and may be unilateral or bilateral. Actual sarcoidosis of the conjunctiva is very rare, occurring in less than 2% of cases. It occurs as small nodules or large follicles scattered irregularly over the palpebral conjunctiva or as rounded outgrowths of pseudogranulation tissue arising from the palpebral conjunctiva. Sarcoid nodules sometimes appear in the episclera, and these episcleral nodules are yellowish red in color and have a predilection for the sites overlying the insertion of the rectus muscles. There has never been any evidence of any true scleral involvement by the disease process. It is also doubtful whether sarcoid ever truly involves the cornea. Corneal changes are frequently associated with sarcoid of the uveal tract, but these changes are usually secondary to the uveitis and apparently represent a degenerative process. Glaucoma, cataracts, and optic

atrophy have been reported in cases of ocular sarcoidosis but are extremely rare. Sarcoid of the orbit is also rare. Reese reports 2 cases out of 355 cases of orbital tumors, while Benedict reported 2 cases out of 1,000 orbital tumors. It is manifest as an orbital tumor usually with a unilateral palpable mass and occasionally with actual proptosis.

Diagnosis

The importance of an early diagnosis cannot be overstressed, and early recognition of the disease depends upon an awareness of the various clinical manifestations. Since the etiology is unknown and there are no specific tests available, it cannot be emphasized too strongly that both clinically and pathologically the diagnosis of sarcoid is one of exclusion. Thus if one sees a granulomatous type of eye disease in which the histologic examination, either by biopsy or by the Kviem test, is compatible with sarcoid and the other known causes of a granuloma can be ruled out, only then is one justified in making a diagnosis of ocular sarcoidosis.

Treatment

Sarcoidosis of the eye has always been resistant to treatment, but the use of steroids now show promise. A large number of agents have been used in the past, including antibiotics, sulfones, radiation, mechlorethamine, and, more recently, calciferol and dihydrotachysterol. Careful evaluation and follow-up studies on patients so treated demonstrated that such therapy has been of little value in sarcoidosis. Intensive treatment with corticotropin, either with the long-acting repository injection (gel) or by intravenous drip, and the parenteral or oral administration of the adrenocorticosteroids have been followed in some cases by almost complete regression of the lesions. On the termination of treatment, approximately 50% of the favorably reacting patients showed prompt recurrence of the clinical symptoms, denoting that prolonged therapy with a low maintenance dose is usually necessary. Woods reported several cases in which, after inital control of the ocular symptoms by intensive corticotropin therapy, the topical use of corticosteroids in the eyes appeared sufficient to prevent local relapse, although recurrence of cutaneous and mediastinal lesions was noted.

Hertzog recently reported on a patient who had sarcoid with systemic manifestations and nodule in the left iris associated with all the signs of active iridocyclitis, such as extensive keratic precipitates, flare, and cells in the anterior chamber; scattered particles of pigment on the lens, and some posterior synechiae. For those who are reluctant to use systemic steroid therapy because of the risk of complications, this case is especially worthy of consideration in view of the large doses and the uncomplicated course. As has been mentioned previously, the usually accepted adequate initial daily dose of prednisone in uveitis is 40 mg. This patient received 35 mg. of prednisone by mouth every six hours, or 140 mg. per day, which is three to four times the usual amount; this dose gradually was increased to 50 mg. every six hours by the 10th day, or five times the usual dose. Treatment was terminated on the 14th day, a rather rapid withdrawal from large doses of steroids. The patient showed no ill effects during treatment or afterwards. The weight remained essentially unchanged. Values for serum albumin, globulin, calcium, phosphates, sodium, chloride, and alkaline phosphates remained normal. No local therapy was used except 2% atropine daily. Because of these large doses of steroids, the patient was given antacids, antispasmodics, supplementary potassium, and a low sodium diet. The results of treatment in this case after two weeks included almost complete absorption of the nodule in the iris, almost complete clearing of the flare and cells, absence of the previous lymphadenopathy and calcification, and roentgenologic evidence of reduction in size of hilar nodes. The uncorrected vision remained 20/20 in both eyes, and the tension remained normal. In the absence of any other effective or

specific therapy, intensive use of steroids appears thoroughly justified in ocular sarcoidosis. It is possible that prolonged oral use of small doses of prednisone also may be useful in preventing recurrence and protecting the eyes once the initial symptoms have been controlled.

12027 Riverside Drive.

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Annual Reviews

The Lens and Vitreous

WILLIAM COUNCILMAN OWENS, M.D., Easton, Pa.

This review of the literature on the lens and vitreous covers the period to December, 1958. However, no attempt has been made to cite every article that has appeared during this time. Only those articles that have interested me most have been included. The general outline of topics is the same as in the summary of the literature for the previous period.

Surgery of the Lens

Preoperative Complications. — Seedorff [1] made a study of the records of 200 cataract patients. Seventy-eight of these patients were in the younger age group (20 to 50 years of age). A definite etiological background for the lens opacities was found in about 70% of the cases in this younger age group. The etiological background cited consisted of diabetes, parathyroid hypofunction, myasthenia, or heterochromia. On the other hand, in the group of patients in the older age group (over 50 years of age), only 11% of the cases had a history of conditions which might have been related to the cataract. It is of importance that the underlying disease be diagnosed and treated if present. Seedorff found that the number of severe operative and postoperative complications, such as loss of vitreous, serious iritis, detachment of the retina, severe hemorrhage, and panophthalmitis, which resulted in greatly impaired vision were also much greater in the younger group than in the group of patients with predominantly senile cataracts. Voisin and Sourdille [2] found that operations on octogenarians were not contraindicated. However, particular attention should be paid to the patient's general health. They recommended light preanesthetic sedation and local injection of anesthetics in this group, and they stressed the importance of corneoscleral sutures, the intracapsular technique, and early ambulation during the postoperative course.

Dollfus, Haye, and Pinchon [3] reported their results in cataract extraction on 94 diabetic patients operated upon in Paris and Rouen. Hyphemas occurred in 16.6% of the Paris series and in 8.7% of the Rouen group. Postoperative iridocyclitis was present in 11.6% of the Paris group and in 15% of the Rouen operations, while glaucoma occurred postoperatively in 8.3% of the Paris cases and in 15% of the Rouen cases.

Confirming the previous report of Stanković and Kecmanović,[4] Sedan [5] found that the zonules in cases with megalocornea are very weak and the cataractous lens can be easily extracted, almost spontaneously, after breaking the friable zonules by light pressure exerted through the cornea at the 6 o'clock position. Ryan [6] recommended the use of the intracapsular technique, with use of the erisophake in dealing with cases of cataract complicated with megalocornea.

The presence of high myopia as a complication of cataract and the best method of handling such cases has always presented a serious problem. Saraux [7] studied the complications and results in cataract operations performed on high myopes. He concluded that detachment of the retina was the most formidable complication encountered, occurring in 8% of the cases he studied. He therefore recommended postponing cataract operation in myopes as long as possible and waiting one year before

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operating on the fellow eye, as a detachment of the retina will most likely appear in the year first after the operation for the cataract. He preferred the extracapsular extraction in the presence of high myopia and recommended a complete iridectomy, so that the fundus can be more easily examined in case a detachment of the retina subsequently occurs.

In the Bedell Lecture, Chandler [8] recommended prompt removal of the lens or any remaining lens material in eyes with lens-induced uveitis and glaucoma. In this excellent article he reviewed the clinical findings in cases with lens-induced uveitis and glaucoma.

Agarwal [9] preferred placing the corneal incision in front of the filtering bleb when cataract extraction must be performed in the presence of a previous antiglaucoma filtering operation. He described 106 operations in which the section was made in front of the filtering bleb. For these cases he used the Stallard suture.

Handling cases in which the cataractous lens has become displaced into the posterior portion of the vitreous chamber is always a difficult problem. Smith [10] reported his experience in such a case. He was able to introduce an erisophake directly into the vitreous cavity, apply it to the cataract, and make the extraction, but he pointed out the dangers involved. Reese and Wadsworth [11] presented pathologic and clinical evidence for the presence of an adhesion between the lens capsule and the hyaloid membrane. Of 20 enucleated eyes tested, they found evidence of such an adhesion in 5 instances. The adhesions may be due to inflammatory processes but are usually developmental. Their presence may lead to rupture of the capsule or loss of vitreous during the operation and to retinal detachment after surgery. If the condition is recognized at operation an erisophake should be used or the adhesions broken "by wedging a spoon between the hyaloid and the capsule with the cornea intervening."

Instruments.—Ebadi [12] described two new instruments. One was a four-pronged corneal fixation forceps. The other was a broad corneal knife curved like a scimitar and designed to prevent the iris from being accidently cut during the section of the cornea. A modification of the Verhoeff forceps was described by Rizzuti.[13] He added a small shelf 3.0 mm. long and 1.5 mm. thick to one blade of the forceps. With this shelf he can retract the iris superiorly just before the forceps are applied to the superior pole of the lens.

Anesthesia.—The tendency to use tranquilizers in conjunction with the other preanesthetic agents is increasing, and more favorable reports are appearing in the literature. Nielsen [14] found the tranquilizer, Perphenazine, useful in 50 operative procedures. Perphenazine 4.0 mg. was given four times a day for two days before operation. One hour before surgery each patient received 10 to 15 mg. of Perphenazine intramuscularly along with 0.1 gm. of secobarbital (Seconal) and 2.0 mg. of levorphanol (Levo-Dromoran). Lorhan and Holman [15] found that cyclizine reduced the incidence of nausea and vomiting. They used 50 mg. of cyclizine intramuscularly in conjunction with 50 mg. of meperidine hydrochloride (Demerol) and 100 mg. of pentobarbital given one hour before operation. Salleras [16] has found the use of promethazine (Phenergan) helpful. For premedication he gave 50 mg. promethazine by intramuscular injection and 100 mg. of Luminal by mouth 12 hours before operation. One and one-half hours before operation he gave 25 mg. chlorpromazine (Thorazine), 50 mg. Phenergan, "one ampule of Demerol and one ampule of the anti-Parkinson drug, diethylamino-2′ methyl-N- dibenzoparathiazine intramuscularly." In addition, Luminal was given according to age and weight. Röser [17] found that a similar preanesthetic preparation not only eliminated the need for a retrobular injection of local anesthetic but produced a favorable circulatory and psychic condition of the patient, with the result that fewer complications occurred.

Some authors have recommended these agents for supplemental intravenous administration at the time of the cataract extraction. Townes and Mann [18] stated that for most patients satisfactory preoperative medication consisted of barbiturates or promethazine hydrochloride (Phenergan) by mouth and meperidine hydrochloride (Demerol) and chlorpromazine hydrochloride (Thorazine) by intramuscular injection. However, in patients who were extremely apprehensive, recalcitrant, deaf, or psychotic, they recommended the use of an intravenously administered supplement at the time of operation. For this purpose they used 1.5 grains of secobarbital (Seconal) the evening before operation, and the dose was repeated two hours before operation. Demerol, 50-75 mg., and 1/300 (0.22 mg.) grain of scopolamine were administered one hour before operation. At operation a mixture of 25 mg. chlorpromazine hydrochloride, 100 mg. of meperidine hydrochloride, and 50 mg. of promethazine hydrochloride in 25 cc. of saline was given intravenously, 1 cc. per minute, until the patient fell asleep. The average dose used was 6.8 cc., and the largest was 13 cc. Oxygen at the rate of 1 liter per minute was administered underneath the drapes. They found the method entirely satisfactory, the only complication being a marked fall in blood pressure in a few cases. Williams [19] reported a similar schedule. He used promethazine hydrochloride 25-50 mg. orally and secobarbital 100 mg. orally the night before operation. On the day of operation promethazine hydrochloride 25-50 mg. was given intramuscularly two hours before operation. Meperidine hydrochloride 25-100 mg. and scopolamine or atropine 0.3 to 0.4 mg. were given intramuscularly one hour before operation. At the time of operation a mixture of 250 mg. of meperidine hydrochloride in 500 cc. of saline (0.05%) was allowed to run intravenously just before the local anesthesia and akinesia were given. The saline mixture was used during the operation as needed, and promethazine hydrochloride 12.5 to 50 mg. was used intravenously if needed.

Some authors still advocate the use of general anesthesia as a routine, and some regimes advocated are very severe. Colding and Carsten [20] recommended general anesthesia for routine cataract extraction. They used sodium pentothal to induce sleep and then curarized the patient until respiratory arrest was obtained. At that point orotracheal intubation and artificial ventilation with nitrous oxide-oxygen mixture were used. Toward the end of the operation Largactil was given intravenously. However, Gartner and Billet [21] sounded a warning on the use of general anesthesia.

Technique.—Virac,[22] a complex of elemental iodine and a cationic detergent with potent germicidal activity, has been found useful as an efficient surgical preparation for the skin. It was not toxic to the human eye and was an excellent solution for irrigating the conjunctival sac and the lacrimal passages.

Atkinson [23] presented an excellent review and summary of the advantages of various techniques and procedures for cataract extraction. Jaffe [24] confirmed the present trend by favoring linear extraction in preference to discission as the operation of choice in developmental cataract. Alves [25] described the technique used in Dr. Heitor Marback's clinic in Bahia, Brazil. He used two scleral fixation 0000 nonabsorbable (silk) surgical sutures, one below and one on the temporal side. The results in 431 cataract extractions are reported. Hartman, Saraux, and Haye [26] reviewed their results in 138 patients in whom the cataract was extracted according to the Kirby technique. In their results, loss of vitreous occurred in only one case. Fechner [27] studied the Smith method of extraction and rejected it but recommended a greater use of expression than is generally used. In his technique, the zonule is ruptured at 6 o'clock by a combination of traction with the forceps and pressure. During the tilting maneuver and in the final stage of extraction, the expressor is used almost exclusively, while

the forceps serves merely to check the degree of deliverance.

Kirsch [28] measured the fall per minute in the intraocular pressure after the application of digital pressure to the eye after retrobulbar injection. He found that the optimum time for the application of digital pressure was five minutes.

McGrath [29] described a technique with an incomplete Graefe section, leaving a corneoscleral bridge intact while sutures are inserted and iridotomies or iridectomies performed. Gormaz [30] recommended a prefashioned shelving incision through the cornea.

In the de Schweinitz Lecture, Dunnington [31] reviewed ocular wound healing and pointed out the role of the epithelial and stromal elements in the mechanism. Weil, Elisaoph, and Laval [32] found that the use of antihistaminics seemed to retard wound healing in rabbits. Escapini [33] described his technique for making the cataract section. He used an incision through the conjunctiva at the limbus.

Kronenberg [34] wrote an interesting review of the variety, composition, and physical characteristics of suture materials and needles used in ophthalmic surgery. Some of the methods of suturing have become very complicated. Ebadi [35] described two new suture methods. The first is a postplaced suture 3 mm. in width parallel to the limbus. One end of the suture is looped under the transverse corneal section of the suture before it is tied. This is supposed to facilitate the subsequent removal of the suture. The second method he described is the use of two continuous sutures of different colored material. One suture is inserted from right to left and the other from left to right. The two are then tied together at their extremities.

Atkinson [36] advocated the use of De-Wecker scissors with blunt ends on both blades for making the peripheral iridotomy. With these scissors the iridotomy can be made without introduction of the iris forceps.

Intraocular Lenticular Substitutes

In this field the battle is still raging. Schillinger, Shearer, and Levy [37] obtained poor results in animals after the implantation of an acrylic lenticulus shaped like a narrow spool, that fits into the pupillary opening and is supported by the iris. Gasteiger [38] analyzed the results obtained in 20 personal cases of implantation of anterior chamber lenses after cataract extraction. Several serious complications occurred, such as epithelial dystrophy, purulent panophthalmitis, and sympathetic ophthalmitis. Postoperatively a longer period of ocular inflammation occurred. He felt that the implantation should not be undertaken in older people and that in younger people the use of a contact lens postoperatively is more satisfactory.

On the other hand, Lieb and Guerry [39,40] reported on the implantation into the anterior chamber of a plastic lens with resilient mounts attached tangentially to the refractive part of the lens. They recommended placing the lens during a secondary operation after the cataract extraction. In the 29 cases they reported, excellent results were obtained.

Contact Lenses

As Gasteiger [38] pointed out, more investigators are exploring the use of contact lenses for monocular aphakia in place of the use of intraocular lenticular substitutes. Westsmith [41] recommended the use of contact lenses for the correction of monocular aphakic refraction errors. However, Ogle, Burian, and Bannon [42] reviewed the optical and physiologic problems that exist with the correction of unilateral aphakia with contact lenses. They pointed out that from theoretical optic considerations it is rarely possible to eliminate aniseikonia even when the unilateral aphakia is corrected by contact lenses. The aniseikonia remaining is usually greater than 9%. The ability of the patients to have comfort in the presence of this residual aniseikonia may be due to (1) poor fusional ability before the development of the cataract, (2) suppression learned after the formation of the cataract, (3) differ-

ences in the visual acuity of the two eyes after removal of the cataract, and (4) the extent to which the patient is satisfied with confused peripheral vision.

Aphakic Refraction

As a temporary lens to be used during the immediate postoperative period, Craig [43] described a 30 mm. lens with a proximal curvature of −6.00 D. sphere and a distal curvature of +18.00 D. sphere. This lens can be attached to the patient's own spectacle lens with cellophane (Scotch) tape, and the final refraction can be done over this lens.

Postoperative Complications

Flat Anterior Chamber.—Posner [44] stated that a flat anterior chamber after cataract extraction is always due to a leaking wound. If the anterior chamber is absent immediately after cataract extraction, the wound should be inspected for the presence of a leak. An external leak may be detected by placing the end of a strip of filter paper directly on the wound. Wherever a leak is present, the filter paper becomes moist. If the cause of the leak is evident, as in the case of a gaping wound or a prolapsed iris, it should be repaired immediately. If no cause is evident, the use of a carbonic anhydrase inhibitor may restore the chamber. Aqueous normally contains a substance which inhibits proliferation of fibroblasts. The leakage of normal aqueous between the wound edges may thus prevent prompt closure of these edges by fibrous tissue. If the anterior chamber is lost several days postoperatively, it is usually due to leakage through a suture tract and the suspected suture should be promptly removed. In cases where the anterior chamber persists in remaining flat, Laval [45] makes a sclerotomy 4 mm. from the limbus and introduces a needle along the inner side of the sclera until it enters the anterior chamber, where air is injected.

Epithelial Invasion.—Payne [46] found that about 15% of the eyes enucleated after cataract extraction were lost because of epithelization of the anterior chamber. He stated that there was no satisfactory treatment for the condition and that emphasis should be placed on its prevention. Regan [47] demonstrated that implanted epithelial cells had to be in contact with the iris stroma if they were to continue to grow in the anterior chamber. She felt that the best prophylaxis against the occurrence of an epithelial invasion was the use of a limbus-based conjunctival flap, corneoscleral sutures which do not pass through more than half of the depth of the incision, and mildly chromicized absorbable sutures instead of silk sutures. The extent to which growth may occur inside the eye was shown by the case reported by Vannas.[49] In his case the eye was removed six months after a combined intracapsular cataract extraction. The epithelium was found to have grown over the anterior chamber and extended back over the ciliary processes onto the anterior portion of the retina.

Infection.—Carli and Autric [50] reported that in Tunisia many of the patients undergoing cataract operation have had frequent external infections, especially trachoma, and that postoperative infections are common. They found that the incidence of postoperative infection can be reduced by the subconjunctival injection of 30,000 units of penicillin and the systemic administration of penicillin and dihydrostreptomycin. Late infection can occur and pass into the interior of the eye through filtering cicatrices. Sugar and Zekman [51] studied the records of 500 consecutive cataract extractions. In five cases they found obviously filtering cicatrices, in spite of the use of three corneoscleral sutures at the time of operation. In two of these five cases infection occurred. The authors recommended the use of five corneoscleral sutures to prevent this complication and advocated the eradication of any filtering blebs that occur with the use of the thermocautery or by direct secondary suturing if necessary. Picó [52] reported his experience with postoperative endophthalmitis. He felt that, although the outlook is gloomy for recovery, the use of chloramphenicol, tetracycline, and prednisone is the

best treatment now available. Foster, Almeda, Littman, and Wilson [53] had the misfortune to experience a case of postoperative endophthalmitis caused by Volutella. For its treatment they used amphotericin B. The intravenous route was first used but abandoned because the level obtained was not effective. They advocated the intraocular injection of 20μg. to 35μg. in a volume of 0.05 ml. every 10 days for a total of three doses. In addition, subconjunctival injection of 15μg. should be given at the same time and a bacitracin ointment containing 5 to 10 mg. of amphotericin B per gram applied each day. With this regime they were able to destroy the fungus infecting the eye, but so much damage had occurred during the course of the infection that phthysis bulbi occurred.

Hemorrhage.—Schrader [54] found that the use of acetazolamide (Diamox) reduced the incidence of postoperative anterior chamber hemorrhage. Pau [55] found that about one-third of the postoperative expulsive hemorrhages occurred during the cataract extraction, about one-third occurred between three and six hours after the operation, and about one-third occurred between seven hours and nine days after the operation. He felt that these proportions indicated that most of the expulsive hemorrhages are not due to a single rupture of a pathologically altered choroidal vessel when the intraocular pressure falls to zero at the time of operation. He stated that, beside local and general changes in the vascular system, an increase of pressure upon the eye and sudden rise of blood pressure may lead to expulsive hemorrhage. The comparatively high number of expulsive hemorrhages occurring between three and six hours after the operation suggested that functional vascular reactions to the operative trauma, such as initial spasm and subsequent dilatation, may be of importance in the etiology of expulsive hemorrhage.

Vitreous Changes.—The changes in the appearance of the vitreous face after cataract extraction were studied by de Roetth.[56] He found that destruction of the hyaloid membrane progresses with age. When the vitreous face is ruptured, glaucoma, retinal detachment, and corneal dystrophy are frequently found. Welch and Cooper [57] suggested that a disturbance of some sort in the vitreous was a partial cause in macular edema occurring after cataract extraction, while postoperative papilledema seemed to be related to hypotony. Goar [58] warned that prompt action should be taken if the hyaloid adheres to the cornea. When this occurs, striae and stromal edema are found. He advocated injection of air into the anterior chamber or, if necessary, a posterior sclerotomy and air injection. If the adhesion persists for 8 to 10 weeks, permanent irreversible changes occur in the cornea.

Removal of Sutures.—The removal of sutures has been leading to some postoperative complications. For this reason, some of the surgeons have been advocating the use of mildly chromicized absorbable sutures and others have been reporting methods for making the removal easier. Esposito [59] advocated the use of DeWecker scissors. Simonton and Blaydes [60] removed the sutures while the patient was in bed. Two pillows beside the patient's head are used to support the surgeon's arms, and an assistant holds the upper lid open with Desmarres lid retractors. Wilson [61] recommends the use of a knife instead of the scissors.

Miscellaneous.—Dorello and Dell' Aquila [62] found that the average corneal astigmatism was 2.308 D. when measured two months after operation in 60 cases studied. The amount of astigmatism was less after cataract extraction than in cases that had undergone filtering operations.

Hervouet [63] described his method for removing capsular remains. First he recommended a preliminary operation during which the iris is freed of any adhesion to the capsular remains. The second operation is performed some days later. Two Paufique needles are used simultaneously, one entering the cornea at 9 and one at

6 o'clock. Each is pressed into the membrane and used to make an opening.

Clinical Observations of the Lens

Congenital Malformations.—Françosis [64] described a new syndrome of congenital cataract and microphthalmia associated with dyscephalia, mandibular aplasia, dental anomalies, nanism, hypotrichosis, and atrophy of the skin. Two Japanese brothers, aged 9 and 12, with cortical cataracts associated with congenital ichthyosis were reported by Pinkerton.[65] A genealogic investigation of floriform cataract led Tosch [66] to the conclusion that the factor was expressed as an autosomal dominant in three generations. The floriform cataract was thought to occupy an intermediate position between the congenital cataracts that become opaque early and those that evolve later in childhood.

Vancea and Lazarescu [67] described two cases of lenticonus, one having changes on both the anterior and posterior poles of the lens.

Cataracts Associated with Metabolic Disorders.—Zonular cataracts were observed in two children born to diabetic mothers.[68] In one case the cataract was detected at 4 months of age, in the other case the cataract was not seen until the patient was over 3 years of age. Granstrom felt that the cause was a disturbance of calcium metabolism in the mothers in connection with their diabetes.

Hartstein [69] observed 12 patients who showed no evidence of cataract formation in spite of the fact that they had received galactose for 2 to 12 months. Wilson and Donnell [70] followed 12 cases with galactosemia for six months to nine years. In eight cases cataracts developed, and in none of these was any regression noted, even though appropriate dietary treatment was instituted immediately after the diagnosis.

Exfoliation of the Lens Capsule.—Gifford [71] reported 64 cases of senile exfoliation of the lens capsule. He distinguished two types. In the "wide-band" type, there was a tendency to glaucoma, while in the "narrow-band" type, there was no tendency to develop glaucoma. In the early stages of the disease, he recommended frequent dilatation of the pupil. If glaucoma is present he recommended a filtering operation unless the lens showed an opacity, when removal of the lens was advocated. From a histologic study of three eyes with exfoliation and six lenses removed from eyes showing exfoliation, he concluded that exfoliation of the lens capsule is a true degeneration of the zonule and zonular lamella of the lens.

The clinical and histopathologic findings in an eye with true exfoliation of the lens capsule due to thermal injury were contrasted with the findings in an eye with pseudoexfoliation of the lens. Callahan and Klien [72] found that the damage in true exfoliation was predominantly in the interfibrillary cement substance.

Miscellaneous.—Clinical examination was made of the eyes of 633 patients in a mental hospital in Finland by Koskenoja and Runeberg.[73] Of these patients, 237 had received electric convulsive therapy. An analysis of the findings showed that electric convulsive therapy was not found to cause electric cataract. Calmettes, Deodati, and Amalric [74] found a case of lens opacities in association with argyrosis, and Gemolotto [75] reported a case of copper cataract secondary to a copper splinter in the vitreous. Besides the sunflower cataract, a star-like opacity was present involving the posterior capsule.

Avasthy and Gupta [76] reported spontaneous clearing of the opacity in a traumatic cataract, and Richards and Ellis [77] described a case of displacement of the lens in a 15-year-old girl after two procedures for retinal detachment, where a band formed to pull the lens posteriorly.

Laboratory Investigations of the Lens

The Normal Lens.—Norrby [78] studied the eyes of 345 rats, aged 16 to 543 days, and found that the lens and the eyeball grow at the same rate during the period studied, while the cornea and longitudinal

axis grew more rapidly in the beginning and began to decrease in rate of growth earlier than the lens and eyeball. After 270 days of age, however, all of the parts of the rat's eye grew at the same rate. The electron microscope had been used to study the anatomy of the lens. Wanko and Gavin [79] studied the lens epithelium. They found that the cell membrane had an irregular shape with many processes. The mitochondria were similar to the basic pattern found in other tissues. The endoplasmic reticulum was scanty. The electron microscope gave little new information on the nucleus. Hueck and Kleifeld [80] studied the lens fibers. They demonstrated that each lens fiber possessed its own distinct membrane and that there was a very small intracellular space between each lens fiber. In addition, very tiny oval structures were identified in the lens fibers.

Hockwin, Neumann, and Kleifeld [81] found qualitative as well as quantitative changes in the protein fractions of the lenses in the embryonic fibers as compared to those of the postembryonic fibers. A decrease in the amount of soluble lens protein was found after a time as short as six days when the animal was placed on a galactose diet by Dische, Zelmenis, and Youlus.[82] During the period of galactose feeding there was a strong accumulation of a protein which precipitated after oxidation with ferricyanide. François and Rabaey [83] used the paper and agar plate methods of electrophoresis to study the composition of lens proteins and the changes that occur in them in the various locations during growth and senescence. However, because he found paper electrophoresis inadequate, Resnik [84] studied the α-crystallin of calf lens by use of the analytical ultracentrifuge, diffusion methods, and moving-boundary electrophoresis. He was able to give many of the physicochemical characteristics of the protein and estimated that it had a molecular weight in the order of magnitude of 1,000,000. Merola and Kinoshita [85,86] studied the concentration of the sulfhydryl group bound to protein and the sulfhydryl groups in glutathione in the normal bovine lens. They found that the concentration of protein sulfhydryl groups was four times greater than the sulfhydryl groups in the glutathione. The protein sulfhydryl groups are stable toward oxidation and apparently are masked in their normal state in the lens, as urea denaturation of the protein is required to activate them in regard to oxidation. They were surprised to find that the nucleus of either the young or adult lens contained a higher concentration of protein sulfhydryl groups than the cortex, which was the reverse finding in regard to glutathione concentration.

Halbert and FitzGerald [87] studied the immunologic organ specificity of the lens proteins by the agar precipitin technique. They prepared rabbit antisera against human, fish, frog, and squid lens and studied the cross precipitations found between the antisera and the lens material of these various species. They were able to identify as many as six lens components in the vertebrate lenses they studied. The invertebrate squid lens was immunologically completely distinct from the vertebrate lenses.

Metabolism of the Normal Lens.—A new method of studying the lens was described by Vogel and Reinoehl.[88] With their instrument small solids and minute quantities of various liquids can be placed into the lens in the living animal. Their technique has been used in studying the power of the lens to reduce methylene blue and in the ability of fluorescein to diffuse.

Tissue culture techniques have been making steady progress. Mamo and Leinfelder [89] found that human lens epithelium would survive and grow in tissue culture for a period of up to 21 days. The best growth was obtained under aerobic conditions. However, under anaerobic condition or in an oxygen-enriched atmosphere, growth was obtained but to a smaller extent than that seen under normal aerobic conditions. Constant [90] described a simplified culture medium for growing whole lenses in vitro. She found that an adequate supply

of buffer was necessary. Wachtl and Kinsey [91] improved the media they use for culturing the whole lens. With the new media an in vivo rate of mitosis of the lens epithelium was maintained for 18 hours and did not decline to 60% of normal until 24 hours. The glucose consumption and lactate production were maintained at constant levels for at least seven days. They found [92] that the rabbit lens cultured in vitro utilized about 3 to 5 mg. of glucose per day and that the quantity consumed was not altered when the concentration of glucose was raised from 125 to 250 mg. %. Galactose and xylose were consumed at about one-half and fructose at about one-fifth this rate. In the case of the latter three sugars, the consumption was increased when the concentration in the media was raised. The utilization of any of the foreign sugars tested was unaffected by the presence of glucose, and glucose consumption continued unaffected by the presence of the foreign sugars in the media. However, the foreign sugars were not capable of supporting appreciable mitotic activity of the lens epithelium.

Farkas and Patterson [93] studied the mode of action of insulin in lens metabolism. They found that the injection of insulin into the rat before death increased the ability of the lens to utilize glucose in vitro. However, the addition of insulin directly to the medium of the lens did not increase the utilization of glucose. Their experiments indicated that the injection of insulin affects an organ, perhaps the liver, or a group of organs, which in turn has an effect on the ability of the lens to consume glucose. Green, Mann, and Paul [94] found a reduction in the bicarbonate ion concentration of the aqueous when the lens in rabbits was removed or became cataractous. They thought this reduction was due to the decreased formation of lactic acid by the cataractous or removed lens.

Kuhlman and Resnik [95] studied quantitatively the presence of various enzymes in the lens capsule, cortex, and nucleus of the newborn rat and of rats at 10 days, 20 days, and 100 days of life. They found that most of the enzymatic activity was present in the capsule and epithelium. During development no major qualitative shifts in the enzymatic activity occurred, although quantitative changes occurred. The presence of a proteinase and of peptidases were demonstrated in the human lens by Zeller and Devi.[96] They found the activity of the proteinase lower in the cataractous lens than in the normal lens.

Experimental Cataract.—The early histopathologic changes in alloxan-induced cataract were found by von Sallmann, Caravaggio, Grimes, and Collins [97] to occur as hydropic swelling of the lens fibers and proliferation of the epithelium. The peripheral layer of germinating cells did not seem to lose its capacity to produce new fibers in the early stages of the lesion. Constant [98] found that a variety of substances would produce inhibition of mitosis of the epithelium or vacuolation in the lens grown in tissue culture. However, the inhibition and the vacuolation did not necessarily parallel each other. The changes produced in vitro by methylene blue resembled most closely the pathologic finding of cataracts produced in vivo.

The glutathione of the rabbit lens was found by de Conciliis [99] to decrease as the lens becomes opaque secondary to anaphylactic uveitis. The observed decrease in glutathione was found to precede the formation of opacities in the lens. A similar reduction in the sulfhydryl groups of the lens was observed in cataracts produced in rats by busulfan (Myleran).[100]

Benedict [101] found that a dose of 100 r of x-ray to the eyes of newborn mice did not produce cataract. If the dose was 200 r, nuclear lens opacities developed, but they sometimes regressed. When the dose was increased to 300 r, lamellar cataracts were produced which rapidly progressed to complete opacification. These radiation effects on the lens of newborn mice were vastly different from the slowly progressing cortical cataracts produced by radiation in older mice.

The Vitreous

By various histologic techniques Szirmai and Balazs [102] studied the distribution of cells in the cortical layers of the vitreous. A regular distribution pattern, perhaps associated with the retinal vessels, was found. The exact function of the cells is not known, but they may be related to the metabolism of hyaluronic acid, since they are embedded in the gel containing the highest known concentration of hyaluronic acid in the normal adult mammalian tissue. Oksala and Lehtinen [103] found that the undamaged healthy vitreous is acoustically homogeneous when tested with ultrasonic waves. However, when the vitreous structure was disturbed by pouring the vitreous into a test tube, it became less homogeneous to ultrasonic waves. This was probably due to the accumulation of thin fibers of the vitreous when the body was disturbed.

Since hormones have been found to have a direct effect on the mucopolysaccharides of the ground substance of tissues, Larsen [104,105] tested the effect of some hormones on the viscosity of the vitreous filtrate obtained from rabbits. Cortisone and the combination of thyroidectomy plus the administration of thyrotropin were found to increase the viscosity of the vitreous and its content of hyaluronic acid. Thyroxin had no effect on the viscosity of the vitreous and reduced its hyaluronic acid content. Ascorbic acid deficiency has also been found to affect the connective tissue, and Cristiansson [106-108] studied the effect of ascorbic acid deficiency of the vitreous. He found a lowering of viscosity and a reduced concentration of glucosamine. There was no quantitative change in the residual protein, but an increase in the water content was observed and a reduction in the orthophosphate content of the vitreous body.

Shafer and Bussey [109] and Reed, Wilt, and Tushingham [110] found that stored human vitreous has an antibacterial substance which provides self-sterilization against inoculation with a variety of bacteria except Bacillus subtilis.

Chandler and Rosenthal [111] found that no significant effect was obtained by the intramuscular injection of trypsin on the absorption of blood from the vitreous of rabbits. This same problem of the absorption of blood from the vitreous has been under investigation by the members of the Proctor Laboratory of the University of California.[112-114] They have been determining the absorption of blood from the vitreous by measuring the rate of decline of radioactivity in the eye after the injection of radioactively tagged blood into the vitreous of rabbits. Various enzymes and surface-acting agents tested by injection into the posterior vitreous were found to be impractical because of the extensive damage they caused. However, it was found that the iron molecule in low molecular weight compounds or in organic compounds produced a marked liquefaction of the vitreous.

Manschot [115] found the presence of preretinal tissue arising from the retinal glial cells in cases of persistent hyperplastic primary vitreous.

There was an unusual report of the appearance of a live, wriggling filaform parasite in the vitreous of a 21-year-old Hindu man. Mishra [116] found that the vision in the involved eye was 6/12 and that there was little inflammatory reaction during the six months of observation. The most refreshing report of the year was given by Post and Post Jr.[117] It should not be overlooked by any one interested in the subject of cataract.

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News and Comment

ANNOUNCEMENTS

Establishment of Committee on the Use of α-Chymotrypsin in Ophthalmology.—At the Annual Meeting of the American Academy of Ophthalmology and and Otolaryngology, a Committee on the Use of α-Chymotrypsin in Ophthalmology was established. The members are Drs. A. E. Maumenee; Ludwig von Sallmann; Richard Troutman, Secretary; David Shoch, and Derrick Vail, Chairman.

The purpose of this Committee is to act as a collector of data on the use of this enzyme by ophthalmologists in the United States and to evaluate the results, in order to determine the hazards, side effects, complications, etc. of its use in cataract surgery.

Correspondence regarding the work of this Committee should be directed to Dr. Richard C. Troutman, 430 E. 63d St., New York 21.

Films for Pan-American Congress of Ophthalmology.—Any person having films on ophthalmological subjects who would desire to show them at the Pan-American Congress of Ophthalmology in Venezuela in 1960 (Jan. 31-Feb. 7) should contact either Dr. Wendell L. Hughes, 131 Fulton Ave., Hempstead, N. Y. or Dr. Louis J. Girard, Hermann Professional Building, Houston 25, Texas, as soon as possible.

Anyone living in South America should contact Dr. Alejandro Salleras of Buenos Aires, Dr. O. Velasquez, Panama, or Dr. R. Valenzuela, Santiago, Chile.

These films should be new films that have not been shown elsewhere. A summary of the film including the title should be sent, along with data as to whether it is silent or sound (optical or magnetic), the length of showing time, and a summary of the subject matter.

Glaucoma Course at Massachusetts Eye and Ear Infirmary.—A one-week course in Glaucoma will be given at the Massachusetts Eye and Ear Infirmary under the direction of Dr. Paul A. Chandler, June 15 through June 20, 1959. Topics to be considered will be ocular hydrodynamics; gonioscopy, tonography, and perimetry; diagnosis, and medical and surgical management. Surgical demonstrations will be held in the operating room. Patients will be available for demonstration and examination. Admission will be limited to 12 persons. Fee: $100.

Application may be made to Dr. E. B. Dunphy, Chief of Ophthalmology, Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston 14.

Course in Clinical Neuro-Ophthalmology.—A course in Clinical Neuro-Ophthalmology will be presented at the Massachusetts Eye and Ear Infirmary on May 17 through 23, 1959 (six days). The instruction will be provided by David G. Cogan, M.D., and associates.

The course will consist of a series of lectures and clinical demonstrations using patient material from the Massachusetts Eye and Ear Infirmary and the Massachusetts General Hospital. Included in the course will be the essentials of ophthalmic neuroanatomy, methods of examination, and the diagnosis of clinical syndromes. Part of the instruction will be in the form of stereophotographs and motion pictures.

The tuition is $100, and the enrollment is limited to 30 members. Inquiries regarding the course may be addressed to Charles Snyder, Registrar, Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston 14.

Annual Examination of Orthoptic Technicians.—The annual examination of orthoptic technicians by the American Orthoptic Council will be conducted in August and October, 1959.

The written examination will be nonassembled and will take place on Thursday, Aug. 20, in certain designated cities and will be proctored by designated ophthalmologists.

The oral and practical examinations will be on Saturday, Oct. 10, in Chicago, just preceding the meeting of the American Academy of Ophthalmology and Otolaryngology.

Application for examination will be received by the office of the Chairman of Examinations, Frank D. Costenbader, M.D., 1605 22d St., N. W., Washington 8, D. C., and must be accompanied by the examination fee of $30. Applications will not be accepted after July 1, 1959.

Books

La Refracción del ojó y sus anomalias. By Dr. E. Gil del Rio. Price, not given. Pp. 592, with 335 illustrations. Editorial "Tip. Cat. Casals," Caspe, 108, Ap. 776, Barcelona, 1957.

Twenty-one chapters are devoted to history of lenses, physical and geometric optics, anatomy of the optical system of the eye, ametropia and defects of the visual system, methods to detect such defects (objective and subjective), corrective lenses, cycloplegics, presbyopia, aphakia, and heterophorias.

The paper is thin, of average quality, and rather poorly printed. The print is small. Copies of portraits of those contributing to this field in previous generations are inadequately reproduced. Color illustrations of fundus lesions are poor.

The discussion on geometric optics is brief, with a minimal number of formulas. The actions of prisms, spheres, and cylinders are presented in the same form and order as in English and American texts in this subject.

Basic principles of refraction by the human eye are given, including the theory of the various types of schematic eyes.

Determination of the objective and subjective refraction of the human eye is discussed in the usual manner and in very adequate fashion, including retinoscopy and various types of refractometers.

The description of methods and apparatus for subjective determination of refraction is excellent.

A brief discussion of contact lenses, neutralization of lenses, bifocal lenses, trifocal lenses, and aniseikonia is given toward the end.

This text is very complete and is very adequate for a student (at the resident level) desiring information on lenses and refraction. No information is included which is not available in English texts.

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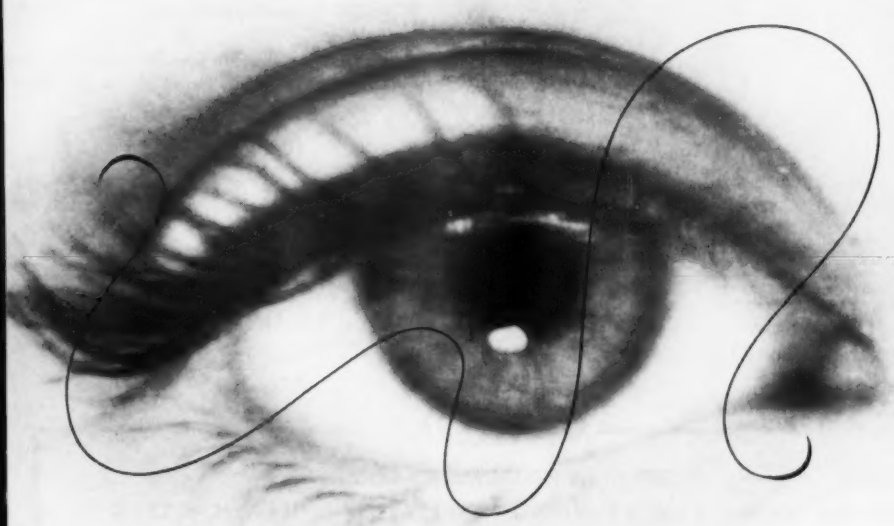

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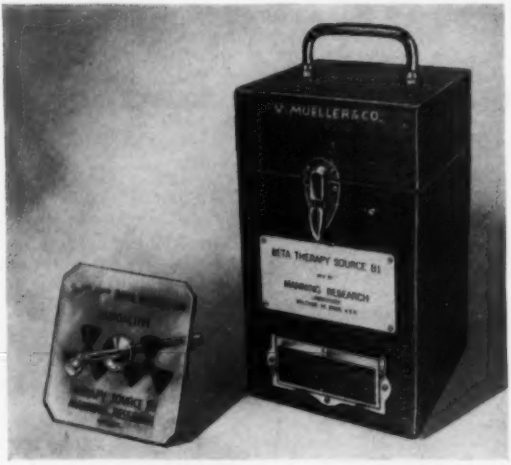

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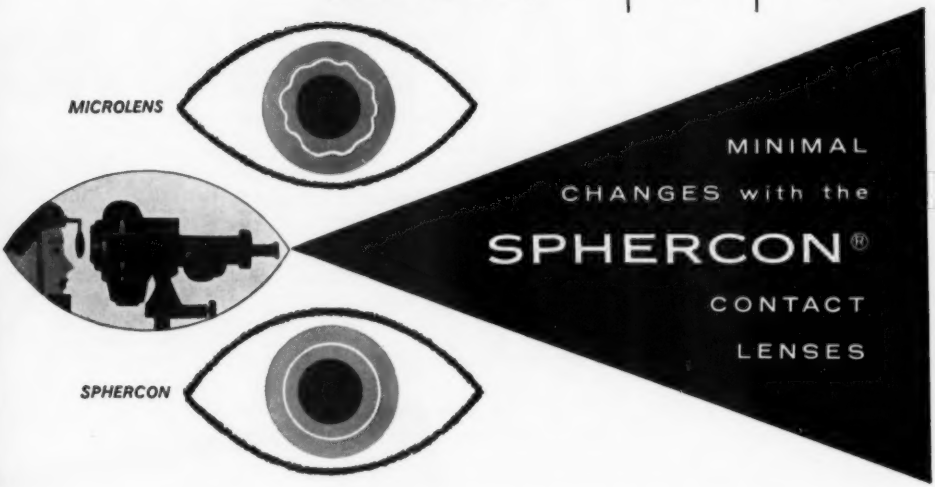

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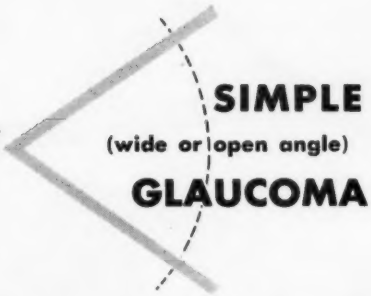

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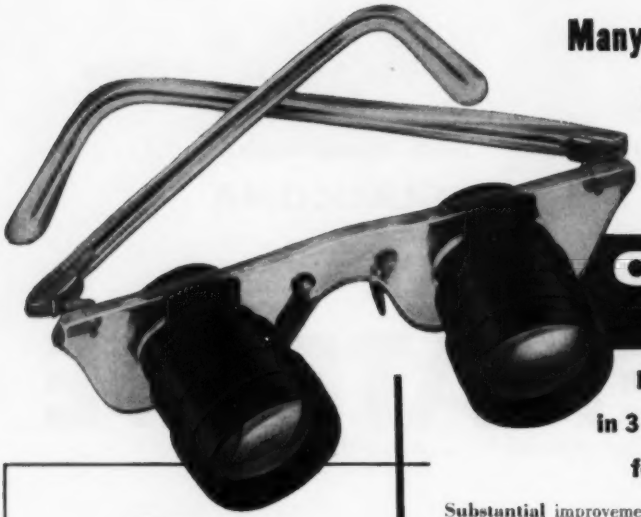

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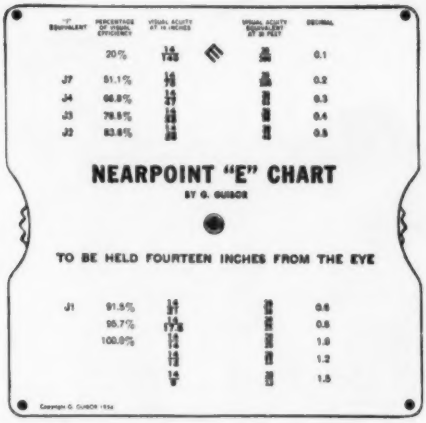

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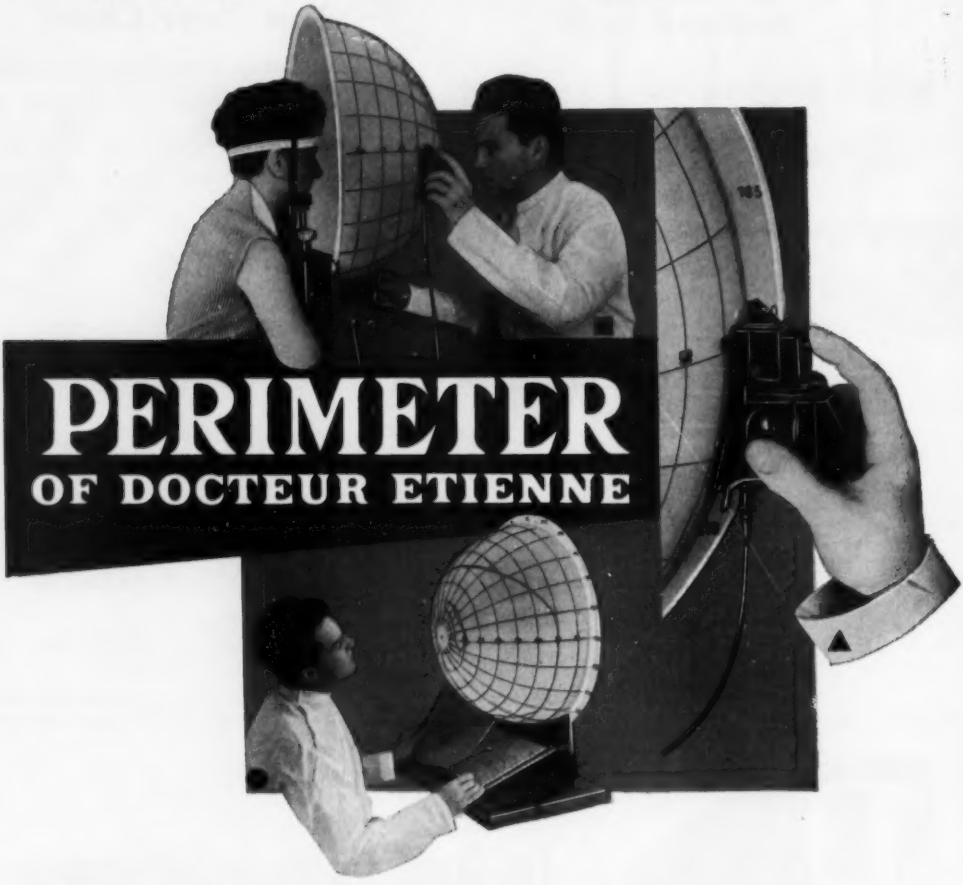

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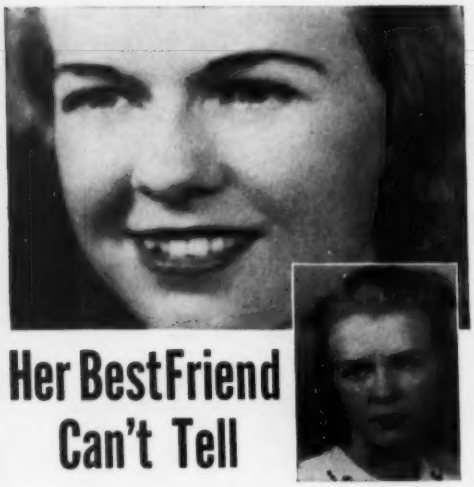

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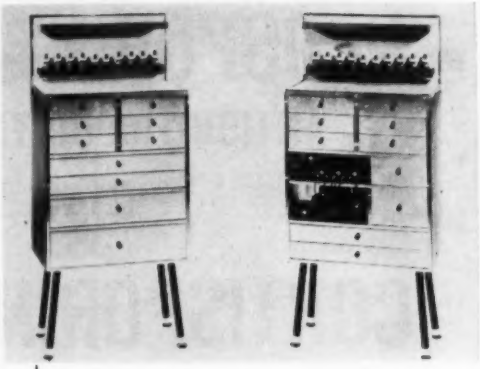

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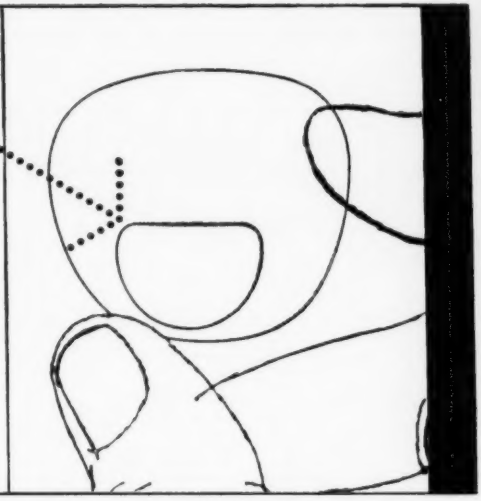

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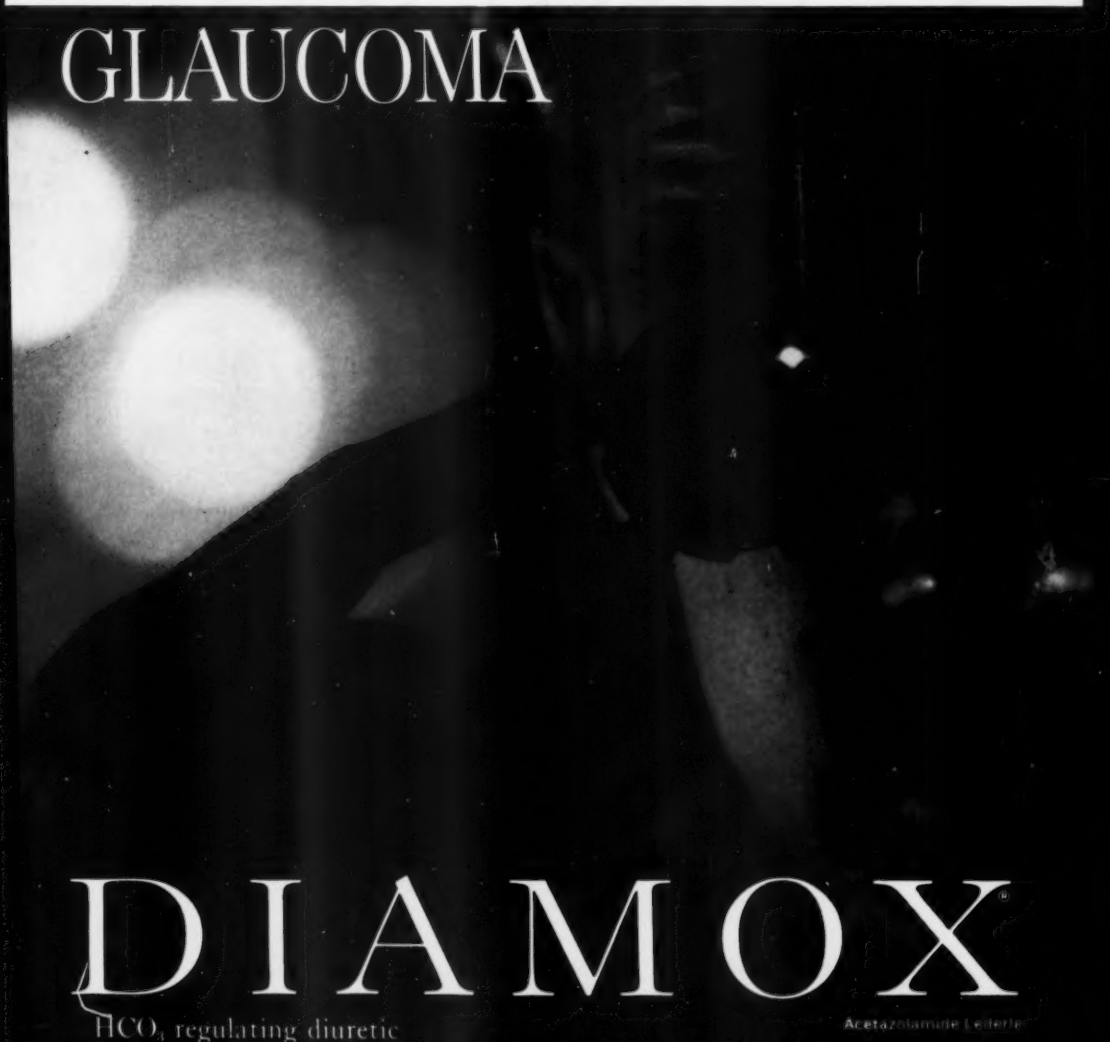
1. Venable, H. P.: J. Nat. M. A., 50:79, 1958.



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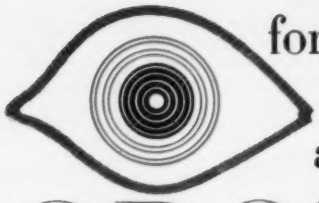

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Indications: Chronic simple (wide angle) glaucoma; acute congestive (narrow angle) glaucoma; chronic congestive glaucoma; secondary glaucoma (acute phase); preoperative control of intraocular pressure of glaucoma.
Dosage: Usual adult dosage is from 25 to 50 mg. once to three or four times daily. Therapy with 'Daranide' is usually most successful when employed in conjunction with miotics. As with patients on any other carbonic anhydrase inhibitor, it is essential to keep a close check on the electrolyte balance of the patient during therapy with 'Daranide'.
Additional information on 'Daranide' is available to physicians on request.
Supplied: 'Daranide' Tablets, 50 mg., bottles of 100.

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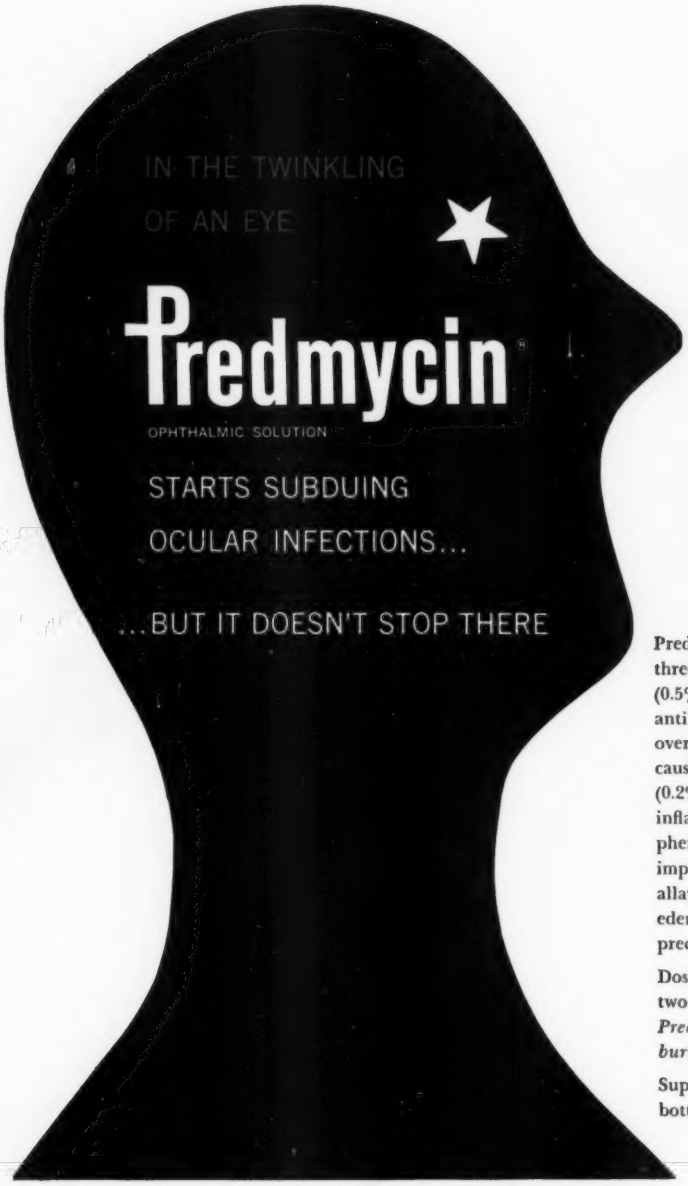

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